IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

ESTELLE GELLER	:	CIVIL ACTION
Plaintiff,	:	
v.	:	NO. 02-4718
WYETH	:	
Defendant.	:	

O R D E R

AND NOW, this _____ day of _____, 2002, upon consideration of Defendant Wyeth's Motion to Dismiss for Failure to State a Claim, and any responses thereto,

IT IS HEREBY ORDERED and DECREED that said Motion is GRANTED and the Complaint of Estelle Geller is DISMISSED for failure to state a claim upon which relief can be granted.

BY THE COURT:

_____
CYNTHIA RUFE, U.S.D.J.

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ESTELLE GELLER	:	CIVIL ACTION
Plaintiff,	:	
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WYETH	:	
Defendant.	:	

DEFENDANT WYETH'S MOTION TO DISMISS THE COMPLAINT OF PLAINTIFF ESTELLE GELLER FOR FAILURE TO STATE A CLAIM

Defendant Wyeth hereby moves this Court, pursuant to Federal Rule of Civil Procedure 12(b)(6), to dismiss the Complaint of plaintiff Estelle Geller for failure to state a claim upon which relief can be granted. The grounds for this Motion are set forth in the accompanying Memorandum of Law, which is incorporated herein by reference.

Respectfully submitted,

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Attorneys for DEFENDANT **WYETH**

DATED: August 14, 2002

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

ESTELLE GELLER	:	CIVIL ACTION
Plaintiff,	:	
v.	:	NO. 02-4718
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MEMORANDUM OF LAW IN SUPPORT OF DEFENDANT WYETH'S MOTION TO DISMISS THE COMPLAINT OF PLAINTIFF ESTELLE GELLER FOR FAILURE TO STATE A CLAIM

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I. INTRODUCTION AND SUMMARY OF ARGUMENT

This case does not belong in court. The Complaint is a cut-paste-and-sign boilerplate filing that copies another complaint (the "Bloch Complaint") filed six days earlier by a different firm on behalf of a plaintiff in Pennsylvania, and which has now been voluntarily dismissed.[1] The Bloch Complaint itself was filed within 48 hours of the release of new data from a long-term study involving Wyeth's hormone replacement drug Prempro™.[2] Like Bloch, this Complaint does not and cannot state any cognizable claim. The inadequate and untenable claims in this Complaint, like Bloch, have more to do with plaintiffs' lawyers racing each other to the courthouse than with tort litigation's legitimate goal of making a plaintiff whole for injury to her.

Here, plaintiff admits that she has no injury and claims only that she "may be" at some unspecified degree of "increased risk of injury" because she used Prempro (Complaint ¶ 4). She used Prempro for "over ten (10) years" but has never been diagnosed with any injury related to Prempro (id.). Yet she purports to represent a class consisting of every woman who has ever used Prempro and seeks (1) personal injury damages, (2) purchase price refunds, (3) an order requiring the defendant to "inform the public" of the reported risks of Prempro, and (4) creation

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1 Bloch v. Wyeth, No. 02-CV-4984 (E.D. Pa. July 22, 2002). The Bloch complaint was originally filed on July 11 in the Philadelphia Court of Common Pleas and removed to this Court on July 22. Wyeth moved to dismiss the Bloch complaint on July 24. Rather than answer Wyeth's motion, Bloch decided to voluntarily dismiss her complaint. The Court approved Bloch's voluntary dismissal on August 8. Although Geller does not assert a statutory claim analogous to Bloch's UTPCPL claim, the purported "substantive" allegations in the Geller complaint are otherwise identical to those in Bloch, right down to the typos and other errors. See note 9 infra.

2 The study is known as the Women's Health Initiative (WHI) study. The new data concerning Prempro was released in an article published in the July 17 issue of the Journal of The American Medical Association (JAMA) and was available on-line on July 9 (Complaint ¶¶ 14-21). As stated in the Complaint, new data caused WHI to terminate the long-term study of Prempro on July 8 (Complaint ¶ 21).

of a court-supervised fund to provide an undefined "medical monitoring" program for some unspecified period of time.

The Complaint should be dismissed. Plaintiff has no basis for any of the relief she seeks. Having suffered no injury, she lacks standing to bring any claim for personal injury. Whether filed as an individual suit or denominated as a class action, a plaintiff has no standing to invoke judicial remedies for injuries suffered – if at all – only by others. See, e.g., O'Shea v. Littleton, 414 U.S. 488 (1974).

Nor does plaintiff's demand for "refunds" or disgorgement based on money paid by consumers for Prempro give rise to any justiciable legal claim. She admits that Prempro never harmed her and that she has not been diagnosed with any injury as a result of Prempro. She also admits that Prempro – which remains on the market and approved by the FDA as "safe and effective"[3] – has been efficacious, i.e., that it effectively replaces hormones lost at menopause and has "thereby reduc[ed] the incidence of post-menopausal symptoms such as hot flashes, night sweats and vaginal dryness" for "millions of women" (Complaint ¶ 10). As courts have recently held, even where a drug has been withdrawn from the market because of safety concerns, a plaintiff who has received the drug's benefits and has suffered no personal injury has no standing to pursue a refund claim on her own behalf or on behalf of anyone else. Rivera v. Wyeth-Ayerst Labs, 283 F.3d 315 (5th Cir. 2002); Lennon v. Wyeth-Ayerst Labs., Inc., No. 1793 EDA 2000, 2001 WL 755944 (Pa. Super. June 14, 2001),[4] alloc. denied, 729 A.2d 1253 (Pa.

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3 See 21 C.F.R. § 314.2 (1998).

4 All unpublished opinions cited herein are in alphabetical order in a separately-filed Appendix.

Dec. 17, 2001) (affirming dismissal of refund suit brought by uninjured recipients of childhood vaccine which had been withdrawn from the market).[5]

There is similarly no merit in plaintiff's request for an order requiring defendant to publicize the "dangers" of Prempro. Plaintiff herself certainly needs no such further communication. Her Complaint attests to her own detailed awareness and sensitivity to the alleged "dangers" of Prempro. And she has no standing to pursue the claims – if any – of other Prempro users who might lack her own heightened awareness. Moreover, the extent to which drug companies inform physicians and/or patients of the risks and benefits of FDA-approved drugs is thoroughly and carefully regulated by the FDA pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. §§ 301 *et seq*. The "package insert," as well as all forms of direct-to-consumer advertising, are subject to pervasive FDA control and oversight. See 21 U.S.C. § 352 and 21 C.F.R. Parts 201 and 202. The FDA also has ample power and the sole discretion to enforce its regulations, including the power to require drug companies to issue whatever revised warning labels or public notices that might be required. 21 U.S.C. §§ 352(f)(2), 336, and 375; 21 C.F.R. §§ 201.56 and 201.57. The FDA can also issue safety warnings itself if company actions are deemed insufficient. 21 U.S.C. § 375. The FDA also provides for "citizen petitions" by which

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5 Not only is Prempro still FDA-approved, still on the market, and admittedly effective in treating post-menopausal systems, the WHI data cited by plaintiff also demonstrates Prempro's value in combating osteoporosis and colorectal cancer (Complaint ¶ 22). Moreover, the National Heart, Lung and Blood Institute ("NHLBI") specifically stated in the news release announcing the termination of the Prempro portion of the WHI study that "for osteoporosis prevention, women should consult their doctors and weigh the benefits against their personal risks for heart attack, stroke, blood clots and breast cancer" and that "women taking the therapy for relief from menopausal symptoms may reap more benefits than risks." WHI, *New Facts About Estrogen/Progestin Hormone Therapy* ("New Facts") attached hereto as "Exhibit A." The Court may consider this publication on a Rule 12(b)(6) motion because it is undisputedly authentic and plaintiff refers in her Complaint to the information and news releases developed by NHLBI in conjunction with the release of the study results (see Complaint ¶ 21). See, e.g., Rossman v. Fleet Bank Nat'l Ass'n, 280 F.3d 384, 388 n.4 (3d Cir. 2002); Pension Benefit Guar. Corp. v. White Consol. Indus. Inc., 998 F.2d 1192, 1196 (3d Cir. 1993); In re Burlington Coat Factory Securities Litig., 114 F.3d 1410, 1426 (3d Cir. 1997); In re MBTE Prod. Liab. Litig., 175 F Supp. 2d 593, 606 n.17 (S.D.N.Y. 2001) (citing Fed. R. Evid. 201(b)(2) and cases).

members of the public can petition the agency to exercise its authority. See 21 C.F.R. § 10.30. Here, plaintiff has not filed any citizen petition and has no standing to usurp the FDA's role as the public's guardian in this regard. See, e.g., Bernhardt v. Pfizer, Inc., 2000 U.S. Dist. LEXIS 16963, at *8-9 (S.D.N.Y. Nov. 16, 2000) (refusing to consider personal injury plaintiff's request for injunction requiring drug company to inform public and physicians of drug's lack of effectiveness).[6]

Finally, plaintiff's demand for a "medical monitoring" program to administer unspecified tests to every past or present user of Prempro also fails to state a viable claim on which relief can be granted. The Florida courts have carefully spelled out the essential elements of a suit for medical monitoring relief and the Complaint makes clear that they cannot be satisfied here.[7] The Florida courts have followed Redland Soccer Club, Inc., v. Dep't of the Army, 548 Pa. 178, 696 A.2d 137 (1997) and Barnes v. American Tobacco Co., 161 F.3d 127, 138 (3d Cir. 1998), and have adopted the same stringent threshold criteria for medical monitoring as Pennsylvania. Petito v. A.H. Robins Co., Inc., 750 So. 2d 103 (Fla. Dist. Ct. App. 1999), review denied, 780 So.2d 912 (Fla. 2001). Medical monitoring costs cannot be imposed on a defendant under Florida law without a showing, *inter alia:* that a defendant's "negligence" caused a plaintiff to be exposed to a "proven hazardous substance;" that "as a proximate result of the exposure," plaintiff has a "significantly increased risk" of contracting "a serious latent disease;" and that a monitoring procedure exists which not only makes early detection of such

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6 In Bernhardt, the court stayed the request for injunctive relief to allow the FDA to consider plaintiff's request while plaintiff's personal injury case continued in court. Here, plaintiff has no personal injury case and has no standing to make a request for injunctive relief. Her Complaint should simply be dismissed.

7 Plaintiff is a Florida citizen, and presumably was prescribed and used Prempro in Florida, so the claims she purports to assert against Wyeth arise and fall under Florida law. See, e.g., Le Jeune v. Bliss-Salem, Inc., 83 F.3d 1069, 1072 (3d Cir. 1996) (discussing choice of law analysis).

latent disease possible, but also is "reasonably necessary" and, perhaps most importantly, is "different from that normally recommended in the absence of the exposure." Petito 750 So. 2d 105-07 (citing and quoting Redland Soccer and Barnes) (emphasis added).

Here, plaintiff's claim for medical monitoring fails, at the pleading stage, for at least three reasons:

First, plaintiff never alleges that Wyeth knew or should have known of the WHI study results that have given rise to this case (Complaint ¶¶ 20-21). A drug company's duty – founded upon negligence principles – is to "adequately" warn prescribing physicians of risks of which it is aware or reasonably should be aware. Buckner v. Allergan Pharm., Inc., 400 So.2d 820, 822 (Fla. Dist. Ct. App. 1981), review denied, 407 So.2d 1102 (Fla. 1981). Because plaintiff does not and cannot allege that Wyeth was negligent in failing to disclose prior to July 2002 new data that the study itself did not release until that time, she cannot allege – and the Complaint does not allege – that her "exposure" to Prempro was proximately caused by Wyeth's negligence. The medical monitoring claim must be denied on this ground alone.

Second, the Complaint fails to allege that plaintiff has a "significantly increased risk" of contracting a serious disease from Prempro (see Complaint ¶¶ 69-70). All plaintiff pleads is that she "may" be at some degree of increased risk (Complaint ¶ 4). Such an allegation is clearly insufficient under Florida law. Moreover, the WHI data relied upon by plaintiff make it clear that no Prempro users could make the requisite allegation, or showing, of "significantly increased risk." The breast cancer data quoted in the Complaint, for example, suggest that long-term use of Prempro might increase a woman's annual risk of breast cancer from .30 of 1% to .38 of 1%, an increase of only eight one-hundredths of 1%, hardly the level of "significantly increased risk" on which a court-imposed medical monitoring program could or should be based.

Third, and perhaps most compelling, the Complaint completely fails to address a fundamental element of the cause of action for medical monitoring. The desired monitoring must be "different from that normally recommended in the absence of the exposure." For example, it is not enough to say that mammograms are useful for the early detection of breast cancer or even that they are "reasonably necessary" for some subset of women. Rather, a plaintiff seeking to shift the cost of such testing to the defendant must allege – and eventually prove – that such testing is "reasonably necessary" because of exposure to the defendant's product and is not something that would be appropriate anyway. Here, the Complaint carefully avoids alleging that the monitoring program envisioned for Prempro users (which the Complaint never bothers to describe) is somehow "different" from that which would be appropriate for menopausal women who never used Prempro (Complaint ¶¶ 68-74). This is not a mere pleading failure. On breast cancer, for example, routine mammography is already standard medical practice for all post-menopausal women. There is no "different" monitoring regimen which plaintiff has alleged – or could allege – that is medically necessary for Prempro users.

No amount of boilerplate can create an injury plaintiff does not have or disguise her lack of standing to obtain the relief she seeks. Her hasty copycat filing disregards the most basic principles of standing and justiciability and fails to satisfy the most basic pleading elements of the claims she purports to bring. Without even reaching the manifest unsuitability of this case for class certification, the Court should dismiss it.

II. ARGUMENT

Plaintiff has no injury, no damages, no standing, and no cognizable tort, contract, or equitable theory for her various claims against Wyeth.[8] Because she has no right under existing law to have the Court entertain her claims, each and every count of her no-injury Complaint should be dismissed under Rule 12(b)(6) for failure to state a claim for relief.

A. Plaintiff Has No Standing To Assert The Claims In Her Complaint

The most glaring infirmity in plaintiff's multi-count Complaint is her inability to plead both injury to herself and causation. This is not just a matter of pleading. It is a matter of constitutional standing and presents an incurable threshold deficiency that puts her out of court on each and every one of the claims she asserts.

The concept of standing derives from the fundamental principle that a plaintiff has no right to sue unless she has suffered some legally cognizable injury caused by defendant's conduct. Allen v. Wright, 468 U.S. 737, 754 (1984); O'Shea, 414 U.S. at 494. The principle is at the cornerstone of any lawsuit – if a plaintiff has no injury or cannot show a causal connection between her alleged injury and defendant's conduct, she has no standing to sue and the Court may not hear her claims. See, e.g., Rivera, 283 F.3d at 318-19.

The courts have not hesitated to dismiss claims for lack of standing where the plaintiff has no legal injury and/or cannot show causation. See, e.g., id.; Lauletta v. Transworld Express, Inc., No. 96-4098, 1998 U.S. Dist. LEXIS 17392, at *8-9 (E.D. Pa. Oct. 29, 1998);

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8 The Complaint has eight counts, numbered I through VIII. Count VII is merely a series of boilerplate assertions regarding intra-corporate liability and does not even purport to state any separate cause of action. Count VIII purports to assert a claim for punitive damages but there is no separate cause of action for punitive damages under Florida law. May v. Fundament, 444 So.2d 1171, 1172 (Fla. Dist. Ct. App. 1984).

Robinson v. Vaughan, No. 91-7646, 1992 U.S. Dist. LEXIS 19518, at *2-3 (E.D. Pa. Dec. 2, 1992). A plaintiff's purported status as a class representative does not change the analysis. See O'Shea, 414 U.S. at 494; Griffin v. Duggen, 823 F.2d 1476, 1483 (11th Cir. 1987); In re MBTE Prod. Liab. Litig., 175 F. Supp. 2d 593, 606-11 (S.D.N.Y. 2001) ("Because La Susa, the only named plaintiff, had no standing at the time the action was commenced and no class has been certified, the entire *La Susa* action must be dismissed"); see also Rink v. Cheminova, Inc., 203 F.R.D. 648, 656 (M.D. Fla. 2001) (class claim requires named plaintiff to have suffered injury that gives rise to claim).

As the Fifth Circuit explained in Rivera, at an "irreducible constitutional minimum" standing has three elements: (1) injury in fact to the plaintiff, (2) a causal connection between the injury and the defendant's conduct, and (3) relief that will redress the injury. 283 F.3d at 318-19 (quoting Lujan v. Defenders of Wildlife, 504 U.S. 555, 560-61 (1992)). Plaintiff does not even get past the first element of the three-part test. She admits that she has used Prempro "for over ten (10) years" without injury (Complaint ¶4). She admits that Prempro has been efficacious in replacing hormones lost at menopause, "reducing the incidence of post-menopausal symptoms such as hot flashes, night sweats and vaginal dryness" for "millions of women," and reducing the risk of colorectal cancer and bone fractures (Complaint ¶¶ 10, 24). Moreover, she does not plead that she (as distinct from other possible users of Prempro) is at any increased risk from her use of Prempro (see Complaint ¶ 4).

Plaintiff cannot hide the fact that she has no cognizable legal injury and no standing by recasting her claims in the boilerplate of tort, contract, and equity. A plaintiff cannot "plead around" the fundamental requirement of threshold injury and standing by asserting the same no-injury claims under different theories. See, e.g., Rivera, 283 F.3d at 320-21. Cf. Martin

v. Ford Motor Co., 914 F. Supp. 1449, 1455 (S.D. Tex. 1996) (granting summary judgment on plaintiff's various tort and statutory counts because they failed to show actual injury); Friends of the Earth, Inc. v. Laidlaw Envntl. Servs. (TOC) Inc., 528 U.S. 167, 180-81 (2000) (plaintiff must demonstrate standing separately for each form of relief sought).

"[O]scillating between tort and contract law claims," the Rivera court observed so incisively, cannot "obscure the fact that [plaintiff] ha[s] asserted no concrete injury. Such artful pleading . . . is not enough to create an injury in fact." Rivera, 283 F.3d at 320-21. The same holds true for plaintiff's inartful and generalized boilerplate pleading. Her pleadings cannot create an injury she does not have or disguise the fact she suffered no cognizable personal or economic harm of any kind from her use of Prempro.

Plaintiff's inability to plead causation also defeats her pretension to standing. She cannot tie the claims she purports to redress or her "exposure" to Prempro to Wyeth's conduct. She does not and cannot allege that Wyeth was negligent in failing to disclose before July 2002 new information about Prempro that was first released at that time.

Although as set forth below plaintiff's claims fail as a matter of law on the merits, the Court need not reach the lack of substantive merit in each and every count of plaintiff's Complaint. The Court may dismiss the Complaint in its entirety because plaintiff cannot get past the standing threshold on any of the claims she purports to assert.

B. Plaintiff Has No Viable Basis Under Florida Law For Any Of The Claims She Asserts

1. Plaintiff's Strict Liability Claim (Count I) Fails As a Matter of Law Because She Has No Injury And No Damages Recoverable In Tort

The generalized boilerplate in Count I of plaintiff's Complaint purports to assert a cause of action in strict product liability based on defective design, defective manufacture,

unspecified misrepresentations, and inadequate warnings (see Complaint ¶¶ 46, 48, 49). Based on these assertions, plaintiff seeks compensatory and punitive damages for an "increased risk of developing injuries" (Complaint ¶¶ 49-50). Although plaintiff's vague boilerplate assertions are plainly inadequate on their face, Count I fails as a matter of law for a more fundamental reason. A plaintiff who has suffered no actual injury from her use of a product does not have a cause of action in tort under Florida law. An increase in risk of injury is not enough to support a tort claim nor is any purported economic loss.

First and foremost, plaintiff's own admissions conclusively defeat her strict liability claim. She admits she has sustained no injury caused by Prempro (Complaint ¶4). Actual injury is an essential element of a strict liability tort claim. West v. Caterpillar Tractor Co., 336 So.2d 80, 86-87 (Fla. 1976); Baker v. Danek Medical, 35 F.Supp.2d 875, 879 (N.D. Fla. 1998). Since plaintiff has no injury, she has no strict liability claim.

The most plaintiff pleads is that she "may be" at an "increased risk of developing injuries" (Complaint ¶4). At its most generous reading, this is not even a prediction of injury. But even if it were, it is no substitute for actual injury. Under established Florida law, a plaintiff cannot recover for an increase in the risk of a disease or injury that she does not have. Eagle-Picher Indus., Inc. v. Cox, 481 So.2d 517, 520 (Fla. Dist. Ct. App. 1986), review denied, 492 So.2d 1331 (Fla. 1986); Landry v. Florida Power & Light Corp., 799 F.Supp. 94, 96 (S.D. Fla. 1992), aff'd, 998 F.2d 1021 (11th Cir. 1993) (citing Eagle-Picher) (rejecting plaintiff's claim of increased risk of cancer, which allegedly resulted from inhalation of radiation dust); see also Petito, 750 So.2d at 105 (confirming validity of Eagle-Picher and distinguishing "injury" element for medical monitoring claim); Simmons v. Philadelphia Asbestos Corp., 674 A.2d 232 (Pa. 1996) (precluding recovery for asbestos-related disease unaccompanied by physical impairment).

The Eagle-Picher court made it clear that predicting future damages is speculative and allowing recovery without a manifest injury is at odds with tort law's goal of redressing injury. Whether "future complication and damage" can be "proved to a reasonable medical certainty, a probability or a possibility, [increased risk] is, no matter what the required quantum of proof, a prediction." Eagle-Picher, 481 So.2d at 524 n.10 (internal citations omitted) (emphasis added). Florida law is clear that plaintiff's no-injury Complaint and her hypothetical claim to an increased risk of injury will not support her strict liability claim in Count I.

Nor can her claim for a refund of the monies she spent for Prempro prescriptions – purported economic damages – supply the missing injury element of her strict liability claim. Florida recognizes the economic loss doctrine, which precludes recovery in tort for purely economic losses that are unaccompanied by personal injury or damage to independent property. McDonough Equip. Corp. v. Sunset Amoco W., Inc., 669 So.2d 300, 302 (Fla. Dist. Ct. App. 1996); Casa Clara Condo. Ass'n, Inc. v. Charley Toppino & Sons, Inc., 588 So.2d 631, 633 (Fla. Dist. Ct. App. 1991), approved by, 620 So.2d 1244 (Fla. 1993) ("[a] plaintiff cannot recover tort damages for purely economic damages"). A plaintiff who has not sustained any personal injury or property damage cannot recover damages in tort. Casa Clara, 588 So.2d at 633.

The economic loss doctrine applies to all actions bottomed in tort, including strict liability. Florida Power & Light Co. v. Westinghouse Elec. Corp., 510 So.2d 899, 901-02 (Fla. 1987)(citing Cedars of Lebanon Hosp. v. European X-Ray Distrib., 444 So.2d 1068 (Fla. Dist. Ct. App. 1984); Casa Clara, 588 So.2d at 633. It applies to and bars plaintiff's strict liability claim in Count I here.

Because plaintiff has no injury and no damages legally cognizable in strict liability, Count I of the Complaint is fatally and incurably deficient. It should be dismissed as a matter of law.

2. Plaintiff Cannot Establish A Negligence Claim As A Matter Of Law (Count II)

Plaintiff's negligence claim in Count II fails for the same reasons as her strict liability claim. First, her boilerplate allegations make it impossible to divine the foundation of her negligence claim. Plaintiff does not describe any action that Wyeth should have taken with respect to Prempro. And she does not allege what, if anything, Wyeth should have, but did not, communicate regarding Prempro. Moreover, even if plaintiff had set forth some failure on the part of Wyeth, she cannot recover under a negligence theory because she has no personal injury and the purely economic losses she claims – even if she had them – are not recoverable in tort.

To establish a cause of action for negligence under Florida law, plaintiff must demonstrate that Wyeth owed a duty of care to her, that Wyeth breached that duty, that Wyeth's breach caused her injury, and that she suffered an actual loss or damage. Strasser v. Yalamanchi, 783 So.2d 1087, 1094 (Fla. Dist. Ct. App. 2001). More specifically, because she is a prescription drug user suing a prescription drug manufacturer for negligence, her theoretical claim would be that Wyeth negligently failed to provide her doctor, who prescribed Prempro, with adequate warnings of the drug's potential dangers. See Felix v. Hoffmann-LaRoche, Inc., 540 So.2d 102, 104 (Fla. 1989)(holding that manufacturer of Accutane, an acne medication, had a duty to warn physicians of any side effects, but it had no duty to warn patients); Baker, 35 at 881 (explaining that "manufacturers of prescription medical products have a duty to warn physicians, rather than patients, of the risks associated with the use of a product").

Plaintiff's pleading on the threshold issues of duty and breach is the same mish-mash of boilerplate allegations copied verbatim from the Bloch complaint, which were themselves apparently extracted from other, unrelated complaints filed by other plaintiffs in other cases.[9] None of the allegations, vague though they are, apply in any respect to this case. Nowhere in her Complaint does plaintiff indicate any way in which Wyeth, the manufacturer in this case, could have been negligent. Her claim is that information was released by NIH about Prempro for the first time in July 2002 as part of a data review of a study of long-term Prempro use in post-menopausal women (Complaint ¶ 21). As a result of the data, the study was discontinued (id.). Plaintiff never alleges – nor could she – that Wyeth had knowledge of the study data prior to July 2002. She cannot assert even one action that Wyeth should have taken but did not take in reaction to data that plaintiff admits was not available to Wyeth until July 2002. Her negligence claim is fatally deficient and should be dismissed on this ground alone.

But even if plaintiff had been able to manufacture some breach on Wyeth's part, her negligence claim would fail because she has no injury and no damages legally cognizable in tort. Actual injury is an essential element of a negligence claim, and it must be pled in the complaint. See Leenen v. Ruttgers Ocean Beach Lodge, Ltd., 662 F. Supp. 240 (S.D. Fla. 1987). Plaintiff cannot recover, as set forth above in Section B.1, for an increased risk of developing an injury in the future. Eagle-Picher, 481 So.2d at 520; Landry, 799 F.Supp. at 96 (rejecting plaintiff's negligence claim where he averred increased risk of injury but failed to demonstrate actual physical injury).

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9 Like Bloch, this Complaint makes the same puzzling accusation (in ¶ 57) that Wyeth continued to market Prempro "when safer and more effective methods of controlling high cholesterol were available" and the same false statement in (¶ 53) that Prempro has been withdrawn from the market. Prempro was never indicated as a means for controlling "high cholesterol" and Prempro remains an FDA-approved drug which continues to be marketed.

Plaintiff's "economic losses" (i.e., her refund claim) are also not recoverable in negligence. She claims no physical injury as a result of taking Prempro. Nor does she claim that Prempro failed to perform for her as she expected. Although she asserts that she is entitled to a refund for amounts she presumably spent on her Prempro prescriptions, this does not save her negligence claim. Under the "long, historic basis" of the economic loss doctrine, "tort law does not impose any duty to manufacture only such products as will meet the economic expectations of purchasers." Florida Power, 510 So.2d at 901-02. "The economic loss rule, simply stated, precludes a recovery in tort for purely economic losses which are unaccompanied by personal injury or damage to independent property." McDonough, 669 So.2d at 302.

Even assuming, then, that plaintiff were able to somehow allege that Wyeth acted negligently, she could not recover under her negligence claim for any increased risk of injury or for money she spent for her Prempro prescriptions. The bottom line is that she cannot establish a breach tied to an injury. Without any personal injury or injury to property other than that which she purchased, she has no legally cognizable claim in negligence. Count II must therefore be dismissed.

3. Established Florida Law Bars Plaintiff's Claims For Unjust Enrichment And Breach of Warranty (Counts III, V, And VI)

Plaintiff obviously recognizes that she has no right to the relief she seeks under traditional tort-based theories because she has no injury. Hence, her novel claim for disgorgement of Wyeth's "wrongful profits, revenue and benefits" under an unjust enrichment theory in Count III and her claim for unspecified compensatory and punitive damages for breach of express and implied warranties in Counts V and VI, respectively. Plaintiff cannot hinge this "no injury/no harm" lawsuit against Wyeth on theories of unjust enrichment or breach of warranty.

First, plaintiff had no dealings with Wyeth that would support a quasi-contractual or equitable claim for unjust enrichment and she cannot point to any unjust benefit Wyeth received as a result of her purchase of Prempro. Plaintiff got an FDA-approved prescription drug for hormone replacement therapy that her physician prescribed for her. She suffered no manifest physical harm and does not even allege that she failed to benefit from her physician-prescribed therapy. How can it be unjust for Wyeth to retain monies derived from the sale of Prempro to her?

Second, plaintiff's lack of privity with Wyeth strikes a fatal blow to plaintiff's contract-based breach of warranty claims. Under Florida law, a plaintiff cannot recover under a breach of warranty claim unless privity of contract exists between the plaintiff and the defendant. Kramer v. Piper Aircraft Corp., 520 So.2d 37 (Fla. 1988). Plaintiff has failed to plead privity – indeed, she cannot – and, consequently, Counts V and VI have no basis in law.

a. Plaintiff's Unjust Enrichment Claim Is Inadequate On Its Face And As A Matter Of Law

Plaintiff's novel unjust enrichment claim contains the same boilerplate that permeates her Complaint and is incurably deficient as a matter of law. As pled, plaintiff's unjust enrichment claim appears to rely on contract-based concepts of implied warranty of merchantability and fitness for use (see Complaint ¶ 66) that do not exist under Florida law because of lack of privity between plaintiff and Wyeth. "Unjust enrichment" or "money had and received" is essentially an equitable doctrine invoked in assumpsit when a party seeks to recover money "erroneously paid or received by a defendant when to permit the defendant to keep the money would unjustly deprive the plaintiff of his ownership of the money." Sharp v. Bowling, 511 So.2d 363, 364-65 (Fla. Dist. Ct. App. 1987).

The doctrine of unjust enrichment does not apply simply because the defendant may have received money or some benefit from some action of the plaintiff. "The mere fact that an overpayment of some sort has been demanded and payment made will not support the [unjust enrichment] action." Hall v. Humana Hosp. Daytona Beach, 686 So.2d 653, 656 (Fla. Dist. Ct. App. 1997), review denied, 694 So.2d 738 (Fla. Apr. 29, 1997) (dismissing unjust enrichment claim brought by class of hospital patients who claimed that the hospital overcharged them for pharmaceuticals and medical supplies); see also Wiernik v. PHH U.S. Mortgage Corp., 736 A.2d 616, 622 (Pa. Super. 1999) (dismissing unjust enrichment claim brought on behalf of class where neither contract nor common law suggested that defendants were unjustly enriched). In other words, unless a plaintiff can plead and show an "unjust" benefit she conferred on the defendant, she has no claim to the quasi-contractual remedy of unjust enrichment and no right to equitable relief.

Here, plaintiff's own admissions defeat her unjust enrichment claim. Payment was not erroneous and was not made directly to Wyeth. Plaintiff got exactly what her physician prescribed, an FDA-approved hormone replacement therapy that caused her no physical harm and which she admits has the known beneficial effects of reducing the incidence of post-menopausal symptoms, hip fractures, and colorectal cancer.

There is nothing unjust in Wyeth's retention of any benefit it may have derived from plaintiff's purchase of Prempro. She is not entitled to get her money back under any theory of unjust enrichment, and Count III of the Complaint should be dismissed.

b. Plaintiff's Inadequately Pled Warranty Claims Fail As A Matter Of Law Because She Lacks Privity With Wyeth

Plaintiff's claims for breach of express and implied warranty in Counts V and VI are both facially deficient and substantively infirm. These claims, like plaintiff's other claims, are nothing more than general boilerplate that no amount of repleading can salvage. Plaintiff does not plead even the most fundamental assertions for recovery for breach of warranty. Moreover, Florida law is clear that a purchaser who has no privity with a manufacturer cannot maintain a claim against the manufacturer based in warranty.

As a matter of threshold pleading, plaintiff's express warranty claim is completely devoid of the prerequisites to an express warranty claim under Fla. Stat. Ann. § 672.313 (2001), i.e., actual affirmations of fact or promises related to Prempro that allegedly became part of the basis of plaintiff's bargain in her decision to purchase Prempro. Plaintiff does not identify a single express warranty that was allegedly directed to her and on which she allegedly relied because she cannot. She does not even allege why she was prescribed and was taking Prempro. And, of course, she admits in the Complaint that Prempro did not cause her any injury or harm. The Court need only take the single word "Prempro" out of paragraphs 76 and 77 to appreciate that plaintiff's allegations could apply to any product and that her purported "express" warranty claim is anything but express; it is completely vague and incapable of comprehension. As for plaintiff's claim for breach of implied warranty, her own admissions expose the palpable deficiency in that claim. Plaintiff alleges that Prempro "would cause severe injuries" when put to its "intended use" (Complaint ¶ 82), but she concedes she has used Prempro for "over ten years" and has not sustained any injury at all.

Although her inadequate pleading and lack of injury are enough to warrant dismissal of her warranty claims, plaintiff has a more fundamental problem. Her lack of privity with Wyeth defeats her warranty claims as a matter of law. To recover for breach of warranty either express or implied under Florida law, a plaintiff must have privity of contract with a defendant. Kramer v. Piper Aircraft Corp., 520 So.2d 37 (Fla. 1988). Claims based in warranty are "purely contract remedies . . . and, accordingly, cannot be maintained in the absence of contractual privity." Affiliates for Evaluation and Therapy, Inc. v. Viasyn Corp., 500 So.2d 688 (Fla. Dist. Ct. App. 1997). Simply put, "[a] plaintiff who purchases a product, but does not buy it directly from the defendant, is not in privity with that defendant." Edgar v. Danek Med., Inc., 1999 WL 1054864, *5 (M.D. Fla. Mar. 31, 1999) (rejecting patient's claim against manufacturer of surgical "bone screws," because the patient did not buy the medical hardware directly from the manufacturer); Baker, 35 F. Supp. 2d at 878-89 (citing Kramer and rejecting breach of implied warranty claim because "Florida courts have required privity between the manufacturer and consumer" since 1988).

This rule has been applied uniformly and consistently to reject warranty claims where there is no privity. See, e.g., T.W.M. v. American Med. Sys., Inc., 886 F. Supp. 842, 844 (N.D. Fla. 1995) (dismissing warranty claim against manufacturer for defective penile implant because plaintiff did not purchase implant from manufacturer and thus had no privity); O'Conner v. Kawasaki Motors Corp., 699 F. Supp. 1538, 1544 (S.D. Fla. 1988) (dismissing implied warranty claim against Kawasaki, regardless of whether it would be characterized as manufacturer or distributor of jet ski involved in accident); Williams v. Bear Stearns & Co., 725 So.2d 397, 400 (Fla. Dist. Ct. App. 1998), review denied, Franklin Resources, Inc. v. Williams, 737 So.2d 550 (Fla. 1999) ("Appellant's contract-based claims, including breach of warranty, are

foreclosed by the lack of privity"); Intergraph Corp v. Stearman, 555 So.2d 1282, 1283 (Fla. Dist. Ct. App. 1990) (reversing judgment awarding compensatory damages for breach of express warranties because buyer had no privity with seller); Westinghouse Corp. v. Ruiz, 537 So.2d 596 (Fla. Dist. Ct. App. 1988) ("A contract action for breach of implied warranty does not lie where there is no privity of contract").[10]

This pervasive and binding authority establishes the futility of plaintiff's warranty claims and mandates their dismissal as a matter of law. Here, plaintiff did not allege that she purchased Prempro directly from Wyeth – nor could she. Plaintiff fails to plead that she had a contractual relationship with Wyeth because she cannot. "Privity" does not appear anywhere in the Complaint because it does not exist. Plaintiff's warranty allegations in Counts V and VI miss the mark as a matter of law and should be dismissed.

4. Plaintiff Does Not And Cannot Allege The Fundamental Prerequisites To A Medical Monitoring Claim Under Florida Law (Count IV)

In their haste to file, plaintiff and her lawyers cut-and-pasted verbatim the medical monitoring claim from the Bloch complaint. Plaintiff's photostatic allegations ignore the pertinent law and do not fit even the most basic requirements for a medical monitoring claim under Florida law.

Florida, like Pennsylvania, recognizes a limited cause of action for medical monitoring. See Petito, 750 So.2d at 106-07. Also like Pennsylvania, Florida requires a plaintiff

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10 Florida's requirement of privity for warranty claims is consistent with the "learned intermediary doctrine," which Florida follows. Under this doctrine, a manufacturer fulfills its duty to warn when it adequately warns physicians of risks associated with a drug. Buckner, 400 So.2d at 822. "This is so because the prescribing physician, acting as a 'learned intermediary' between the manufacturer and the consumer, weighs the potential benefits against the dangers in deciding whether to recommend the drug to meet the patient's needs." Felix, 540 So.2d at 104.

who wants to have a defendant pay for her future "medical monitoring" to plead and prove all of the following seven criteria:

> (1) exposure greater than normal background levels;
>
> (2) to a proven hazardous substance;
>
> (3) caused by the defendant's negligence;
>
> (4) as a proximate result of the exposure, plaintiff has a significantly increased risk of contracting a serious latent disease;
>
> (5) a monitoring procedure exists that makes the early detection of the disease possible;
>
> (6) the prescribed monitoring regimen is different from that normally recommended in the absence of the exposure; and
>
> (7) the prescribed monitoring regimen is reasonably necessary according to contemporary scientific principles.

Id. at 145-46 (quoting Barnes, 161 F.3d at 127, 138-39).

At the pleading stage, it is clear that plaintiff's medical monitoring claim must be dismissed on at least three grounds: (a) her failure and inability to allege exposure caused by defendant's negligence, (b) her failure and inability to allege that she has a "significantly increased risk of contracting a serious latent disease," and (c) her failure and inability to plead a monitoring regimen that is "different from that normally recommended in the absence of the exposure." Petito, 750 So. 2d at 106-107.

a. Plaintiff Does Not And Cannot Allege "Exposure" To Prempro As A Result Of Negligence By Wyeth

As Wyeth details in the earlier sections of this Brief, it is clear from plaintiff's boilerplate Complaint that she has no claim in negligence against Wyeth. This is a fundamental and fatal flaw that requires dismissal of her medical monitoring claim as a matter of law. See Rink, 203 F.R.D. at 661; Wagner v. Anzon, Inc., 684 A.2d 570, 576 (Pa. Super. 1996) (where

there is no negligence, a claim for medical monitoring must fail); Hansen v. Mountain Fuel Supply Co., 858 P.2d 970, 979 (Utah 1993) ("the plaintiff must prove that the exposure to the toxic substance was caused by the defendant's negligence, i.e., by the breach of a duty owed to the plaintiff").

Wyeth's duty under well-established Florida law was to inform prescribing physicians of risks that Wyeth knew about or should have been aware of. See Buckner, 400 So.2d at 822. Plaintiff does not, and could not, allege that Wyeth previously knew or could have known of information that was only first available when the results of the WHI study were made public. Indeed, allegations of the Complaint affirmatively negate any negligence on Wyeth's part (see Complaint ¶¶ 19-20) (acknowledging that prior to the new NIH data, there was no indication or signal of any increased risk, and that the study data on which her case is built have just been realized "for the first time"). On their face and in substance, these allegations are insufficient as a matter of law to support plaintiff's claim for medical monitoring. As Judge Scirica wrote in Barnes, "[i]n order to prevail on their medical monitoring . . . plaintiffs must demonstrate that defendants caused their exposure to tobacco. . . . [B]ut plaintiffs cannot prove causation by merely showing that smoking cigarettes causes cancer and other diseases." 161 F.3d at 144-45 (emphasis added). Plaintiff does not and cannot adequately allege that her exposure to Prempro was due to Wyeth's negligence and that alone bars her medical monitoring claim.

b. Plaintiff Fails To And Cannot Allege That She Is At Any Significantly Increased Risk Of Harm

Plaintiff has not alleged that she is at any, much less a significant, increased risk of harm due to her ingestion of Prempro. To the contrary, all she has alleged is that she "may"

be at some degree of increased risk of injury (Complaint ¶ 4). Such an allegation is plainly inadequate under the Petito criteria.

Even if plaintiff were to allege – which she has not – that other persons are at "significantly increased risk," her own failure to allege that she is would require dismissal of her medical monitoring claim. But it is also clear, based on the data on which plaintiff relies in her Complaint, that no Prempro users are at the sort of increased risk which could justify medical monitoring relief. As to other members of the putative class, the Complaint acknowledges that the risk to each of them is "low" (id. at ¶ 22). Indeed, the absolute and relative risk data quoted in the Complaint make it clear that whatever degree of risk Prempro users face for breast cancer, stroke, heart attacks or blood clots, it is (a) very small and (b) predominantly due to factors other than Prempro. On breast cancer, for example, the data set forth in paragraphs 22-27 of the Complaint suggest that if 10,000 women used Prempro, 38 would get breast cancer, 30 of whom would simply represent a background rate. In other words, according to the Complaint, the use of Prempro might increase a woman's risk of breast cancer from .30 of 1% to .38 of 1%, an increase in the actual risk of eight one-hundredths of 1%.[11] On that sliver of alleged, added risk, plaintiff would require defendant to pay perpetually for the monitoring of millions of women, even though the great majority of the cases which might be detected in any given year would have no relationship whatsoever to any conduct of the defendant.

In the absence of proof that there is a "significant" increased risk of contracting a serious disease, courts have routinely denied broad claims for medical monitoring damages. See,

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11 See WHI, "Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women," JAMA, July 17, 2002, Vol. 288, No. 3, 321, 327 (attached hereto as Exhibit "B"). In fact, the confidence intervals reported in the study mean that the slightly higher incidence of breast cancer in the study is not statistically significant. Id. at 326 and Table.

e.g., Abuan v. General Elec. Co., 3 F.3d 329 (9th Cir. 1993) (granting summary judgment on medical monitoring claim where experts could not quantify increased risk of serious disease as "substantial"); Rink, 203 F.R.D. at 662 n.10, 664 (finding medical monitoring inappropriate where plaintiffs presented "no clear evidence . . . for significantly increased risk of an identified serious latent disease" from exposure to a chemical, which undisputedly posed some health risks); O'Neal v. Dep't of the Army, 852 F. Supp. 327, 328 n.8 (E.D. Pa. 1994) (increased risk of .03% held to be insufficient); Lilley v. Board of Supervisors of La. State Univ. & Agric. & Mech. Coll., 735 So. 2d 696, 705-06 (La. Ct. App. 1999).

Plaintiff's failure and inability to allege, as required by Petito, that she has a "significantly increased risk" of suffering a serious latent disease bars the medical monitoring relief she seeks.

c. Plaintiff Does Not And Cannot Allege The Need For Any Monitoring That Is Different From What Would Otherwise Be Prescribed For Post-Menopausal Women

A claim for medical monitoring requires a party to show that the prescribed monitoring regimen is different from that normally recommended in the absence of the exposure." Rink, 203 F.R.D. at 661 n.8 (quoting Petito, 750 So.2d at 106-07). Plaintiff does not allege – nor could she – that whatever monitoring program she is seeking would be different from that normally recommended for Prempro users, i.e., for menopausal women, in the absence of Prempro.

This is a fatal and incurable defect in her claim for medical monitoring. In Rink, where putative class members were exposed to a suspected carcinogen, the court stated:

> Even in a light favorable to the Plaintiffs, so varied are the facts surrounding each individual's exposure, so varied are the individual reactions of persons exposed to malathion in this fashion, and so uncertain are the long term health consequences of this type exposure, only something in the nature of a general clinic

> … would suffice to meet all the individualized assessment needs of the putative class members. Such a program would in actuality be more akin to a study than to a monitoring program, and this appears entirely unsupported in the law as a separate cause of action.

203 F.R.D. at 662 (emphasis added).

Other courts have consistently ruled in the same manner, rejecting monitoring programs that do not deviate from normal health monitoring in absence of exposure to the risk. See, e.g., In re Paoli R.R. Yard PCB Litig., 2000 WL 274262 (E.D. Pa. Mar. 7, 2000) (denying plaintiff's motion for reconsideration on the exclusion of expert testimony regarding medical monitoring because, *inter alia*, monitoring protocol was the same as what would be recommended for any person, regardless of alleged chemical exposure); Heller v. Shaw Indus., Inc., 1997 WL 535163 (E.D. Pa. 1997), aff'd, 167 F.3d 146 (3d Cir. 1999) (granting summary judgment on medical monitoring claim where plaintiffs failed to show that "increased risks of harm caused by their exposure to toxic substances warrant a change in the medical monitoring that otherwise would be prescribed for [them]"); Arch v. American Tobacco Co., 175 F.R.D. 469, 490 (E.D. Pa. 1997) ("The fact that [plaintiff] smokes would not require any additional monitoring for heart disease not already warranted by the multiple, significant risk factors for heart disease he already has"); Miranda v. Shell Oil Co., 17 Cal. App. 4th 1651, 1660 (1993) ("a toxic tort plaintiff may not recover for preventative medical care and checkups to which members of the public at large should prudently submit"); Hansen, 858 P.2d at 980 ("plaintiff may recover [for medical monitoring] only if the defendant's wrongful acts increased the plaintiff's incremental risk of incurring the harm produced by the toxic substance enough to warrant a change in the medical monitoring that otherwise would be prescribed for that plaintiff, a change that would represent increased costs to the plaintiff"); Potter v. Firestone Tire and

Rubber Co., 863 P.2d 795, 825 (Cal. 1993) (plaintiffs may recover for medical monitoring "only if the evidence establishes the necessity, as a direct consequence of the exposure in issue, for specific monitoring beyond that which an individual should pursue as a matter of general good sense and foresight").

Plaintiff alleges only that "monitoring and testing procedures exist which make the early detection and treatment of disease possible and beneficial" (Complaint ¶ 72). She refrains from alleging, however, that such procedures are any different from those recommended for women of menopausal age as part of a regular monitoring program. This is not a mere oversight or pleading deficiency. The Report of the U.S. Preventive Services Task Force ("USPSTF"), published in Guide to Clinical Preventive Serv., 2d ed. (1996), for example, notes that the American Cancer Society, American College of Radiology, American Medical Association, American College of Obstetricians and Gynecologists, as well as a number of other organizations, recommend annual screening with mammography and a clinical breast exam for all women beginning at age 50. Id. at p. 81.[12] The U.S. Department of Health and Human Services recently reaffirmed the USPSTF guidelines extending the routine mammography recommendation to all women over the age of 40. See HHS Press Release dated Feb. 21, 2002 (attached hereto as Exhibit "D"). As to other alleged risks (i.e., heart attack, stroke, clotting), plaintiff does not even hypothesize what monitoring might be useful or "reasonably necessary according to contemporary scientific principles." See, e.g., Redland Soccer, 696 A.2d at 146.

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12 These guidelines are cited in Paoli, 2000 WL 274262, at *8, as a "widely recognized and authoritative source." Copies of the pertinent sections of the Guidelines are attached hereto as Exhibit "C." Wyeth is permitted to attach these public records to this Motion to Dismiss without converting the motion to a summary judgment motion, as they are "capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned." See cases cited at n. 5, *supra*.

Because plaintiff has utterly failed to describe the monitoring program she thinks is required and because she has further failed to allege that it differs in any way from that normally recommended for women of menopausal age, her medical monitoring claim must be dismissed.

III. CONCLUSION

For all the reasons set forth above, the Complaint in this case fails to state any cause of action upon which relief could be granted. Accordingly, the Complaint should be dismissed.

Respectfully submitted,

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DATED: August 14, 2002

EXHIBIT A

The Women's Health Initiative

New Facts About: ESTROGEN/PROGESTIN HORMONE THERAPY

Choosing whether or not to use post-menopausal hormone therapy is one of the most important health decisions women face as they age. On July 9, 2002, new findings were released about the type of postmenopausal hormone therapy that uses estrogen plus progestin. The findings offer women important new guidance in considering this type of postmenopausal hormone therapy.

The findings come from the Women's Health Initiative (WHI), a 15-year study of ways to prevent heart disease, breast and colorectal cancer, and osteoporosis. WHI, which consists of a set of clinical studies and an observational study, began in 1991 and involves more than 161,000 healthy postmenopausal women. WHI is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with other units of the National Institutes of Health.

One of the clinical studies involved 16,608 women with a uterus who took either estrogen plus progestin therapy or a placebo (a substance that looks like the real drug but has no biologic effect). The main goal was to see if the therapy would help prevent heart disease and hip fractures. Another goal was to see if those possible benefits were greater than the possible risks for breast cancer, endometrial cancer, and blood clots.

The study was stopped early because after 5.2 years the therapy's risks outweighed and outnumbered its benefits.

Another WHI study seeks to answer the same questions for estrogen-only therapy and continues, with results expected in 2005.

Understanding The Results

Results from the estrogen plus progestin study are given in the box. They show that the therapy did not protect against heart disease but actually increased heart attacks, stroke, and blood clots. It also increased the chance of breast cancer. It produced some benefits too: It reduced the risk of colorectal cancer and bone fractures.

It's important to understand that these increased risks apply to an entire population. Women should not be unduly alarmed by the results. The increased risk for an individual woman would be small. For instance, each woman in the study who took the estrogen plus progestin therapy had an increased risk of breast cancer of less than a tenth of 1 percent per year.

Study Results:

Estrogen/progestin therapy resulted in a 26% increase in breast cancer, which caused the study to be stopped. No increase in deaths from breast cancer occurred from the combined therapy--or in deaths from other causes.

Estrogen/progestin therapy also resulted in:

- 41% increase in strokes
- 29% increase in heart attacks
- Doubled rates of blood clots in legs and lungs
- 37% less colorectal cancer
- 34% fewer hip fractures and 24% less total fractures

Recommendations

The new findings allow the following recommendations for estrogen plus progestin use:

First, the therapy should not be continued or started to prevent heart disease. Women should consult their doctor about other methods of prevention, such as lifestyle changes, and cholesterol- and blood pressure-lowering drugs.

Second, for osteoporosis prevention, women should consult their doctor and weigh the benefits against their personal risks for heart attack, stroke, blood clots, and breast cancer. Alternate treatments also are available to prevent osteoporosis and fractures.

Third, women should keep up with their regular schedule of mammograms and breast self-examinations.

Finally, while short-term use was not studied, women taking the therapy for relief of menopausal symptoms may reap more benefits than risks. Women should talk with their doctor about their personal risks and benefits.

For More Information

To learn more about the WHI or heart-related issues, contact the NHLBI Health Information Center at P.O. Box 30105, Bethesda, MD 20824-0105, or (301) 592-8573. Or check the NHLBI Web site at www.nhlbi.nih.gov.

NATIONAL INSTITUTES OF HEALTH * National Heart, Lung, and Blood Institute

 NHLBI Home  WHI Page  Estrogen+Progestin Page

Please send us your feedback, comments, and questions
by using the appropriate link on the page, Contact the NHLBI.

Note to users of screen readers and other assistive technologies:
Please report any accessibility problems here.

EXHIBIT B

ORIGINAL CONTRIBUTION JAMA-EXPRESS

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women

Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.

Design Estrogen plus progestin component of the Women's Health Initiative, a randomized controlled primary prevention trial (planned duration, 8.5 years) in which 16 608 postmenopausal women aged 50-79 years with an intact uterus at baseline were recruited by 40 US clinical centers in 1993-1998.

Interventions Participants received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in 1 tablet (n=8506) or placebo (n=8102).

Main Outcomes Measures The primary outcome was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome. A global index summarizing the balance of risks and benefits included the 2 primary outcomes plus stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63 (0.43-0.92) with 112 cases; endometrial cancer, 0.83 (0.47-1.47) with 47 cases; hip fracture, 0.66 (0.45-0.98) with 106 cases; and death due to other causes, 0.92 (0.74-1.14) with 331 cases. Corresponding HRs (nominal 95% CIs) for composite outcomes were 1.22 (1.09-1.36) for total cardiovascular disease (arterial and venous disease), 1.03 (0.90-1.17) for total cancer, 0.76 (0.69-0.85) for combined fractures, 0.98 (0.82-1.18) for total mortality, and 1.15 (1.03-1.28) for the global index. Absolute excess risks per 10000 person-years attributable to estrogen plus progestin were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while absolute risk reductions per 10000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the global index was 19 per 10000 person-years.

Conclusions Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women. All-cause mortality was not affected during the trial. The risk-benefit profile found in this trial is not consistent with the requirements for a viable intervention for primary prevention of chronic diseases, and the results indicate that this regimen should not be initiated or continued for primary prevention of CHD.

JAMA. 2002;288:321-333 www.jama.com

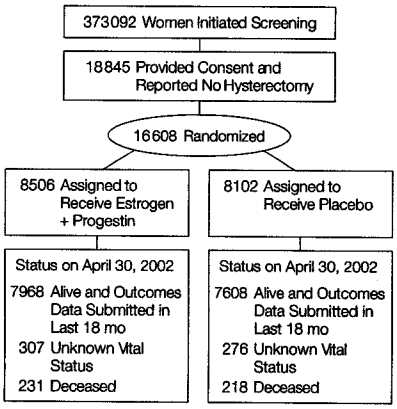
THE WOMEN'S HEALTH INITIATIVE (WHI) focuses on defining the risks and benefits of strategies that could potentially reduce the incidence of heart disease, breast and colorectal cancer, and fractures in postmenopausal women. Between 1993 and 1998, the WHI enrolled 161 809 postmenopausal women in the age range of 50 to 79 years into a set of clinical trials (trials of low-fat dietary pattern, calcium and vitamin D supplementation, and 2 trials of postmenopausal hormone use) and an observational study at 40 clinical centers in the United States.[1] This article reports principal results for the trial of combined estrogen and progestin in women with a uterus. The trial was stopped early based on health risks that exceeded health benefits over an average follow-up of 5.2 years. A parallel trial of estrogen alone in women who have had a hysterectomy is being continued, and the planned end of this trial is March 2005, by which time the average follow-up will be about 8.5 years.

The WHI clinical trials were designed in 1991-1992 using the accumulated evidence at that time. The primary outcome for the trial of estrogen plus progestin was designated as coronary heart disease (CHD). Potential cardioprotection was based on generally

For editorial comment see p 366.

Author Information and Financial Disclosures appear at the end of this article.

Figure 1. Profile of the Estrogen Plus Progestin Component of the Women's Health Initiative



supportive data on lipid levels in intermediate outcome clinical trials, trials in nonhuman primates, and a large body of observational studies suggesting a 40% to 50% reduction in risk among users of either estrogen alone or, less frequently, combined estrogen and progestin.[2-5] Hip fracture was designated as a secondary outcome, supported by observational data as well as clinical trials showing benefit for bone mineral density.[6,7] Invasive breast cancer was designated as a primary adverse outcome based on observational data.[3,8] Additional clinical outcomes chosen as secondary outcomes that may plausibly be affected by hormone therapy include other cardiovascular diseases; endometrial, colorectal, and other cancers; and other fractures.[3,6,9]

The effect of hormones on overall health was an important consideration in the design and conduct of the WHI clinical trial. In an attempt to summarize important aspects of health benefits vs risks, a global index was defined as the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other causes. Compared with total mortality, which may be too insensitive, this index assigns additional weight to the 7 listed diseases. Procedures for monitoring the trial involved semiannual comparisons of the estrogen plus progestin and placebo groups with respect to each of the elements of the global index and to the overall global index.

This report pertains primarily to estrogen plus progestin use among healthy postmenopausal women, since only 7.7% of participating women reported having had prior cardiovascular disease. During the course of the WHI trial, the Heart and Estrogen/progestin Replacement Study (HERS) reported its principal results.[10] HERS was another blinded, randomized controlled trial comparing the same regimen of estrogen plus progestin with placebo among women with a uterus; however, in HERS, all 2763 participating women had documented CHD prior to randomization. The HERS findings of no overall effect on CHD but an apparent increased risk in the first year after randomization seemed surprising given preceding observational studies of hormone use in women with CHD.[3] Subsequent to HERS, some investigators reanalyzed their observational study data and were able to detect an early elevation in CHD risk among women with prior CHD[11-13] but not in ostensibly healthy women,[14] prompting speculation that any early adverse effect of hormones on CHD incidence was confined to women who have experienced prior CHD events.

The WHI is the first randomized trial to directly address whether estrogen plus progestin has a favorable or unfavorable effect on CHD incidence and on overall risks and benefits in predominantly healthy women.

METHODS

Study Population

Detailed eligibility criteria and recruitment methods have been published.[1] Briefly, most women were recruited by population-based direct mailing campaigns to age-eligible women, in conjunction with media awareness programs. Eligibility was defined as age 50 to 79 years at initial screening, postmenopausal, likelihood of residence in the area for 3 years, and provision of written informed consent. A woman was considered postmenopausal if she had experienced no vaginal bleeding for 6 months (12 months for 50- to 54-year-olds), had had a hysterectomy, or had ever used postmenopausal hormones. Major exclusions were related to competing risks (any medical condition likely to be associated with a predicted survival of <3 years), safety (eg, prior breast cancer, other prior cancer within the last 10 years except nonmelanoma skin cancer, low hematocrit or platelet counts), and adherence and retention concerns (eg, alcoholism, dementia).

A 3-month washout period was required before baseline evaluation of women using postmenopausal hormones at initial screening. Women with an intact uterus at initial screening were eligible for the trial of combined postmenopausal hormones, while women with a prior hysterectomy were eligible for the trial of unopposed estrogen. This report is limited to the 16608 women with an intact uterus at baseline who were enrolled in the trial component of estrogen plus progestin vs placebo. The protocol and consent forms were approved by the institutional review boards for all participating institutions (see Acknowledgment).

Study Regimens, Randomization, and Blinding

Combined estrogen and progestin was provided in 1 daily tablet containing conjugated equine estrogen (CEE), 0.625 mg, and medroxyprogesterone acetate (MPA), 2.5 mg (Prempro, Wyeth Ayerst, Philadelphia, Pa). A matching placebo was provided to the control group. Eligible women were randomly assigned to receive estrogen plus progestin or placebo after eligibility was established and baseline assessments made (FIGURE 1). The randomization procedure was developed at the WHI Clinical Coordinating Center and implemented locally through a distributed study database, using a randomized permuted block algorithm, stratified by clinical center site and age group. All study medication bottles had a unique bottle number and bar code to allow for blinded dispensing.

Initially, the design allowed women with a uterus to be randomized to receive unopposed estrogen, estrogen plus progestin, or placebo. After the release of the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial results[15] indicating that long-term adherence to unopposed estrogen was not feasible in women with a uterus, the WHI protocol was changed to randomize women with a uterus to only estrogen plus progestin or placebo in equal proportions. The 331 women previously randomized to unopposed estrogen were unblinded and reassigned to estrogen plus progestin. These women are included in the estrogen plus progestin group in this report, resulting in 8506 participants in the estrogen plus progestin group vs 8102 in the placebo group. Analysis of the data excluding the women randomized before this protocol change did not affect the results. Considerable effort was made to maintain blinding of other participants and clinic staff. When required for safety or symptom management, an unblinding officer provided the clinic gynecologist, who was not involved with study outcomes activities, with the treatment assignment.

Follow-up

Study participants were contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence. Follow-up for clinical events occurred every 6 months, with annual in-clinic visits required. At each semiannual contact, a standardized interview collected information on designated symptoms and safety concerns, and initial reports of outcome events were obtained using a self-administered questionnaire. Adherence to study interventions was assessed by weighing of returned bottles. The study protocol required annual mammograms and clinical breast examinations; study medications were withheld if safety procedures were not performed, but these participants continued to be followed up. Electrocardiograms were collected at baseline and at follow-up years 3 and 6.

Data Collection, Management, and Quality Assurance

All data were collected on standardized study forms by certified staff according to documented study procedures. Study data were entered into a local clinical center database developed and maintained by the Clinical Coordinating Center and provided to each site in the form of a local area network connected to the Clinical Coordinating Center through a wide area network. Data quality was ensured through standard data entry mechanisms, routine reporting and database checks, random chart audits, and routine site visits.

Maintenance/Discontinuation of Study Medications

During the trial, some flexibility of the dosages of both estrogen and progestin was allowed to manage symptoms such as breast tenderness and vaginal bleeding. Vaginal bleeding was managed according to an algorithm that accounted for the time since randomization, severity of the bleeding, treatment assignment, and endometrial histology. Women who had a hysterectomy after randomization for indications other than cancer were switched to unopposed estrogen or the corresponding placebo without unblinding. These women are included in the original randomization group for analyses.

Permanent discontinuation of study medication was required by protocol for women who developed breast cancer, endometrial pathologic state (hyperplasia not responsive to treatment, atypia, or cancer), deep vein thrombosis (DVT) or PE, malignant melanoma, meningioma, triglyceride level greater than 1000 mg/dL (11.3 mmol/L), or prescription of estrogen, testosterone, or selective estrogen-receptor modulators by their personal physician. Medications were temporarily discontinued in participants who had acute myocardial infarction (MI), stroke, fracture, or major injury involving hospitalization, surgery involving use of anesthesia, any illness resulting in immobilization for more than 1 week, or any other severe illness in which hormone use is temporarily inappropriate.

Outcome Ascertainment

Cardiovascular Disease. Coronary heart disease was defined as acute MI requiring overnight hospitalization, silent MI determined from serial electrocardiograms (ECGs), or CHD death. The diagnosis of acute MI was established according to an algorithm adapted from standardized criteria[16] that included cardiac pain, cardiac enzyme and troponin levels, and ECG readings. The primary analyses included both definite and probable MIs as defined by the algorithm. Myocardial infarction occurring during surgery and aborted MIs were included. An aborted MI was defined as chest pain and ECG evidence of acute MI at presentation, an intervention (eg, thrombolysis) followed by resolution of ECG changes, and all cardiac enzyme levels within normal ranges. Silent MI was diagnosed by comparing baseline and follow-up ECGs at 3 and 6 years after randomization. Coronary death was defined as death consistent with CHD as underlying cause plus 1 or more of the following: preterminal hospitalization with MI within 28 days of death, previous angina or MI and no potentially lethal noncoronary disease, death resulting from a procedure related to coronary artery disease, or death certificate consistent with CHD as the underlying cause. Stroke diagnosis was based on rapid onset of a neurologic deficit lasting more than 24 hours, supported by imaging studies when available. Pulmonary embolism and DVT required clinical symptoms supported by relevant diagnostic studies.

Cancer. Breast, colorectal, endometrial, and other cancers were confirmed by pathological reports when available. Current data indicate that at least 98% of breast, colorectal, and endometrial cancers and 92% of other cancers were documented with pathological reports.

Fractures. Reports of hip, vertebral, and other osteoporotic fractures (including all fractures except those of

Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants (N = 16 608) by Randomization Assignment*

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value†
Age at screening, mean (SD), y	63.2 (7.1)	63.3 (7.1)	.39
Age group at screening, y			
50-59	2839 (33.4)	2683 (33.1)	.80
60-69	3853 (45.3)	3657 (45.1)	
70-79	1814 (21.3)	1762 (21.7)	
Race/ethnicity			
White	7140 (83.9)	6805 (84.0)	.33
Black	549 (6.5)	575 (7.1)	
Hispanic	472 (5.5)	416 (5.1)	
American Indian	26 (0.3)	30 (0.4)	
Asian/Pacific Islander	194 (2.3)	169 (2.1)	
Unknown	125 (1.5)	107 (1.3)	
Hormone use			
Never	6280 (73.9)	6024 (74.4)	.49
Past	1674 (19.7)	1588 (19.6)	
Current‡	548 (6.4)	487 (6.0)	
Duration of prior hormone use, y			
<5	1538 (69.1)	1467 (70.6)	.25
5-10	426 (19.1)	357 (17.2)	
≥10	262 (11.8)	253 (12.2)	
Body mass index, mean (SD), kg/m²§	28.5 (5.8)	28.5 (5.9)	.66
Body mass index, kg/m²			
<25	2579 (30.4)	2479 (30.8)	.89
25-29	2992 (35.3)	2834 (35.2)	
≥30	2899 (34.2)	2737 (34.0)	
Systolic BP, mean (SD), mm Hg	127.6 (17.6)	127.8 (17.5)	.51
Diastolic BP, mean (SD), mm Hg	75.6 (9.1)	75.8 (9.1)	.31
Smoking			
Never	4178 (49.6)	3999 (50.0)	.85
Past	3362 (39.9)	3157 (39.5)	
Current	880 (10.5)	838 (10.5)	
Parity			
Never pregnant/no term pregnancy	856 (10.1)	832 (10.3)	.67
≥1 term pregnancy	7609 (89.9)	7233 (89.7)	
Age at first birth, y‖			
<20	1122 (16.4)	1114 (17.4)	.11
20-29	4985 (73.0)	4685 (73.0)	
≥30	723 (10.6)	621 (9.7)	
Treated for diabetes	374 (4.4)	360 (4.4)	.88
Treated for hypertension or BP ≥140/90 mm Hg	3039 (35.7)	2949 (36.4)	.37
Elevated cholesterol levels requiring medication	944 (12.5)	962 (12.9)	.50
Statin use at baseline¶	590 (6.9)	548 (6.8)	.66
Aspirin use (≥80 mg/d) at baseline	1623 (19.1)	1631 (20.1)	.09
History of myocardial infarction	139 (1.6)	157 (1.9)	.14
History of angina	238 (2.8)	234 (2.9)	.73
History of CABG/PTCA	95 (1.1)	120 (1.5)	.04
History of stroke	61 (0.7)	77 (1.0)	.10
History of DVT or PE	79 (0.9)	62 (0.8)	.25
Female relative had breast cancer	1286 (16.0)	1175 (15.3)	.28
Fracture at age ≥55 y	1031 (13.5)	1029 (13.6)	.87

continued

the ribs, chest/sternum, skull/face, fingers, toes, and cervical vertebrae) were routinely ascertained. All fracture outcomes were verified by radiology reports. Study radiographs were not obtained to ascertain subclinical vertebral fractures.

This report is based on outcomes adjudicated by clinical center physician adjudicators, as used for trial-monitoring purposes. Clinical center physician adjudicators were centrally trained and blinded to treatment assignment and participants' symptoms. Future communications will report results based on centrally adjudicated outcomes and will include a broader range of outcomes with more extensive explanatory analyses. Since this report is presented before the planned study closeout, outcome information is still being collected and adjudicated. Local adjudication is complete for approximately 96% of the designated self-reported events. To date, agreement rates between local and central adjudication are: MI, 84%; revascularization procedures, 97%; PE, 89%; DVT, 84%; stroke, 94%; invasive breast cancer, 98%; endometrial cancer, 96%; colorectal cancer, 98%; hip fracture, 95%; and specific cause of death, 82%. When related cardiovascular conditions are combined (eg, when unstable angina or congestive heart failure is grouped with MI), agreement rates exceed 94% for cardiovascular disease and 90% for specific cause of death.

Statistical Analyses

All primary analyses use time-to-event methods and are based on the intention-to-treat principle. For a given outcome, the time of event was defined as the number of days from randomization to the first postrandomization diagnosis, as determined by the local adjudicator. For silent MIs, the date of the follow-up ECG applied. Participants without a diagnosis were censored for that event at the time of last follow-up contact. Primary outcome comparisons are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox proportional haz-

ards analyses,[17] stratified by clinical center, age, prior disease, and randomization status in the low-fat diet trial.

Two forms of CIs are presented, nominal and adjusted. Nominal 95% CIs describe the variability in the estimates that would arise from a simple trial for a single outcome. Although traditional, these CIs do not account for the multiple statistical testing issues (across time and across outcome categories) that occurred in this trial, so the probability is greater than .05 that at least 1 of these CIs will exclude unity under an overall null hypothesis. The adjusted 95% CIs presented herein use group sequential methods to correct for multiple analyses over time. A Bonferroni correction for 7 outcomes as specified in the monitoring plan (described herein) was applied to all clinical outcomes other than CHD and breast cancer, the designated primary and primary adverse effect outcomes, and the global index. The adjusted CIs are closely related to the monitoring procedures and, as such, represent a conservative assessment of the evidence. This report focuses primarily on results using the unadjusted statistics and also relies on consistency across diagnostic categories, supportive data from other studies, and biologic plausibility for interpretation of the findings.

Data and Safety Monitoring

Trial monitoring guidelines for early stopping considerations were based on O'Brien-Fleming boundaries[18] using asymmetric upper and lower boundaries: a 1-sided, .025-level upper boundary for benefit and 1-sided, .05-level lower boundaries for adverse effects. The adverse-effect boundaries were further adjusted with a Bonferroni correction for the 7 major outcomes other than breast cancer that were specifically monitored (CHD, stroke, PE, colorectal cancer, endometrial cancer, hip fracture, and death due to other causes). The global index of monitored outcomes played a supportive role as a summary measure of the overall balance of risks and benefits. Trial monitoring for early stopping considerations was conducted semiannually by an independent data and safety monitoring board (DSMB). Aspects of the monitoring plan have been published.[19]

Table 1. Baseline Characteristics of the Women's Health Initiative Estrogen Plus Progestin Trial Participants (N = 16 608) by Randomization Assignment* (cont)

Characteristics	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	P Value
Gail model 5-year risk of breast cancer, %			
<1	1290 (15.2)	1271 (15.7)	.64
1-<2	5384 (63.3)	5139 (63.4)	
2-<5	1751 (20.6)	1621 (20.0)	
≥5	81 (1.0)	71 (0.9)	
No. of falls in last 12 mo			
0	5168 (66.2)	5172 (67.5)	.18
1	1643 (21.0)	1545 (20.2)	
2	651 (8.3)	645 (8.4)	
≥3	349 (4.5)	303 (4.0)	

*Data are presented as number (percentage) of patients unless otherwise noted. BP indicates blood pressure; CABG/PTCA, coronary artery bypass graft/percutaneous transluminal coronary angioplasty; DVT, deep vein thrombosis; and PE, pulmonary embolism.
†Based on χ^2 tests (categorical variables) or *t* tests (continuous variables).
‡Required a 3-month washout prior to randomization.
§Total number of participants with data available was 8470 for estrogen plus progestin and 8050 for placebo.
‖Among women who reported having a term pregnancy.
¶Statins are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors.

RESULTS

Trial Monitoring and Early Stopping

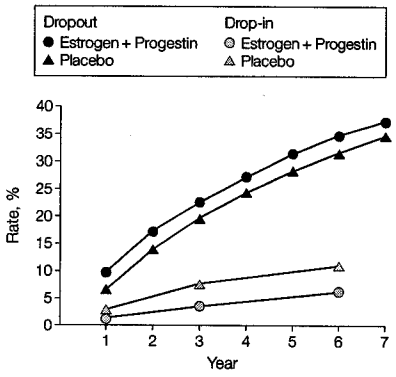
Formal monitoring began in the fall of 1997 with the expectation of final analysis in 2005 after an average of approximately 8.5 years of follow-up. Late in 1999, with 5 interim analyses completed, the DSMB observed small but consistent early adverse effects in cardiovascular outcomes and in the global index. None of the disease-specific boundaries had been crossed. In the spring of 2000 and again in the spring of 2001, at the direction of the DSMB, hormone trial participants were given information indicating that increases in MI, stroke, and PE/DVT had been observed and that the trial continued because the balance of risks and benefits remained uncertain.

In reviewing the data for the 10th interim analyses on May 31, 2002, the DSMB found that the adverse effects in cardiovascular diseases persisted, although these results were still within the monitoring boundaries. However, the design-specified weighted log-rank test statistic for breast cancer (z=−3.19) crossed the designated boundary (z=−2.32) and the global index was supportive of a finding of overall harm (z=−1.62). Updated analyses including 2 months of additional data, available by the time of the meeting, did not appreciably change the overall results. On the basis of these data, the DSMB concluded that the evidence for breast cancer harm, along with evidence for some increase in CHD, stroke, and PE, outweighed the evidence of benefit for fractures and possible benefit for colon cancer over the average 5.2-year follow-up period. Therefore, the DSMB recommended early stopping of the estrogen plus progestin component of the trial. Because the balance of risks and benefits in the unopposed-estrogen component remains uncertain, the DSMB recommended continuation of that component of the WHI. Individual trial participants have been informed.

Baseline Characteristics

There were no substantive differences between study groups at baseline; 8506 women were randomized into the estrogen plus progestin group and 8102 into the placebo group (TABLE 1). The mean (SD) age was 63.3 (7.1) years. Two thirds of the women who reported prior or current hormone use had taken combined hormones and one third had used unopposed estrogen.

Figure 2. Cumulative Dropout and Drop-in Rates by Randomization Assignment and Follow-up Duration



Dropout refers to women who discontinued study medication; drop-in, women who discontinued study medication and received postmenopausal hormones through their own clinician.

Prevalence of prior cardiovascular disease was low and levels of cardiovascular risk factors were consistent with a generally healthy population of postmenopausal women. An assessment of commonly studied breast cancer risk factors, both individually and combined using the Gail model,[20] indicate that the cohort in general was not at increased risk of breast cancer.

Follow-up, Adherence, and Unblinding

Vital status is known for 16025 randomized participants (96.5%), including 449 (2.7%) known to be deceased. A total of 583 (3.5%) participants were lost to follow-up or stopped providing outcomes information for more than 18 months. The remaining 15576 (93.8%) provided recent outcome information (Figure 1).

At the time of this report, all women had been enrolled for at least 3.5 years, with an average follow-up of 5.2 years and a maximum of 8.5 years. A substantial number of women had stopped taking study drugs at some time (42% of estrogen plus progestin and 38% of placebo). Dropout rates over time (FIGURE 2) exceeded design projections, particularly early on, but compare favorably with community-based adherence to postmenopausal hormones.[21] Some women in both groups initiated hormone use through their own clinician (6.2% in the estrogen plus progestin group and 10.7% in the placebo group cumulatively by the sixth

Table 2. Clinical Outcomes by Randomization Assignment*

Outcomes	No. of Patients (Annualized %) Estrogen + Progestin (n = 8506)	Placebo (n = 8102)	Hazard Ratio	Nominal 95% CI	Adjusted 95% CI
Follow-up time, mean (SD), mo	62.2 (16.1)	61.2 (15.0)	NA	NA	NA
Cardiovascular disease†					
CHD	164 (0.37)	122 (0.30)	1.29	1.02-1.63	0.85-1.97
CHD death	33 (0.07)	26 (0.06)	1.18	0.70-1.97	0.47-2.98
Nonfatal MI	133 (0.30)	96 (0.23)	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183 (0.42)	171 (0.41)	1.04	0.84-1.28	0.71-1.51
Stroke	127 (0.29)	85 (0.21)	1.41	1.07-1.85	0.86-2.31
Fatal	16 (0.04)	13 (0.03)	1.20	0.58-2.50	0.32-4.49
Nonfatal	94 (0.21)	59 (0.14)	1.50	1.08-2.08	0.83-2.70
Venous thromboembolic disease	151 (0.34)	67 (0.16)	2.11	1.58-2.82	1.26-3.55
Deep vein thrombosis	115 (0.26)	52 (0.13)	2.07	1.49-2.87	1.14-3.74
Pulmonary embolism	70 (0.16)	31 (0.08)	2.13	1.39-3.25	0.99-4.56
Total cardiovascular disease	694 (1.57)	546 (1.32)	1.22	1.09-1.36	1.00-1.49
Cancer					
Invasive breast	166 (0.38)	124 (0.30)	1.26	1.00-1.59	0.83-1.92
Endometrial	22 (0.05)	25 (0.06)	0.83	0.47-1.47	0.29-2.32
Colorectal	45 (0.10)	67 (0.16)	0.63	0.43-0.92	0.32-1.24
Total	502 (1.14)	458 (1.11)	1.03	0.90-1.17	0.86-1.22
Fractures					
Hip	44 (0.10)	62 (0.15)	0.66	0.45-0.98	0.33-1.33
Vertebral	41 (0.09)	60 (0.15)	0.66	0.44-0.98	0.32-1.34
Other osteoporotic‡	579 (1.31)	701 (1.70)	0.77	0.69-0.86	0.63-0.94
Total	650 (1.47)	788 (1.91)	0.76	0.69-0.85	0.63-0.92
Death					
Due to other causes	165 (0.37)	166 (0.40)	0.92	0.74-1.14	0.62-1.35
Total	231 (0.52)	218 (0.53)	0.98	0.82-1.18	0.70-1.37
Global index§	751 (1.70)	623 (1.51)	1.15	1.03-1.28	0.95-1.39

*CI indicates confidence interval; NA, not applicable; CHD, coronary heart disease; MI, myocardial infarction; CABG, coronary artery bypass grafting; and PTCA, percutaneous transluminal coronary angioplasty.
†CHD includes acute MI requiring hospitalization, silent MI determined from serial electrocardiograms, and coronary death. There were 8 silent MIs. Total cardiovascular disease is limited to events during hospitalization except venous thromboembolic disease reported after January 1, 2000.
‡Other osteoporotic fractures include all fractures other than chest/sternum, skull/face, fingers, toes, and cervical vertebrae, as well as hip and vertebral fractures reported separately.
§The global index represents the first event for each participant from among the following types: CHD, stroke, pulmonary embolism, breast cancer, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes.

year). These "drop-in" rates were also greater than expected.

At the time of this report, clinic gynecologists had been unblinded to treatment assignment for 3444 women in the estrogen plus progestin group and 548 women in the placebo group, primarily to manage persistent vaginal bleeding. During the trial, 248 women in the estrogen plus progestin group and 183 in the placebo group had a hysterectomy.

Table 3. Cause of Death by Randomization Assignment

	No. (Annualized %)	
	Estrogen + Progestin (n = 8506)	Placebo (n = 8102)
Total deaths	231 (0.52)	218 (0.53)
Adjudicated deaths	215 (0.49)	201 (0.49)
Cardiovascular	65 (0.15)	55 (0.13)
Breast cancer	3 (0.01)	2 (<0.01)
Other cancer	104 (0.24)	86 (0.21)
Other known cause	34 (0.08)	41 (0.10)
Unknown cause	9 (0.02)	17 (0.04)

Intermediate Cardiovascular Disease End Points

Blood lipid levels, assessed in an 8.6% subsample of fasting blood specimens collected from women at baseline and year 1, showed greater reductions in low-density lipoprotein cholesterol (−12.7%) and increases in high-density lipoprotein cholesterol (7.3%) and triglycerides (6.9%) with estrogen plus progestin relative to placebo (data not shown), consistent with HERS and PEPI.[10,22] Systolic blood pressure was, on average, 1.0 mm Hg higher in women taking estrogen plus progestin at 1 year, rising to 1.5 mm Hg at 2 years and beyond (data not shown). Diastolic blood pressures did not differ.

Clinical Outcomes

Cardiovascular Disease. Overall CHD rates were low (TABLE 2). The rate of women experiencing CHD events was increased by 29% for women taking estrogen plus progestin relative to placebo (37 vs 30 per 10000 person-years), reaching nominal statistical significance (at the .05 level). Most of the excess was in nonfatal MI. No significant differences were observed in CHD deaths or revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty). Stroke rates were also higher in women receiving estrogen plus progestin (41% increase; 29 vs 21 per 10000 person-years), with most of the elevation occurring in nonfatal events. Women in the estrogen plus progestin group had 2-fold greater rates of venous thromboembolism (VTE), as well as DVT and PE individually, with almost all associated CIs excluding 1. Rates of VTE were 34 and 16 per 10000 person-years in the estrogen plus progestin and placebo groups, respectively. Total cardiovascular disease, including other events requiring hospitalization, was increased by 22% in the estrogen plus progestin group.

Cancer. The invasive breast cancer rates in the placebo group were consistent with design expectations. The 26% increase (38 vs 30 per 10000 person-years) observed in the estrogen plus progestin group almost reached nominal statistical significance and, as noted herein, the weighted test statistic used for monitoring was highly significant. No significant difference was observed for in situ breast cancers. Follow-up rates for mammography were comparable in the estrogen plus progestin and placebo groups. Colorectal cancer rates were reduced by 37% (10 vs 16 per 10000 person-years), also reaching nominal statistical significance. Endometrial cancer incidence was not affected, nor was lung cancer incidence (54 vs 50; HR, 1.04; 95% CI, 0.71-1.53) or total cancer incidence.

Fractures. This cohort experienced low hip fracture rates (10 per 10000 person-years in the estrogen plus progestin group vs 15 per 10000 person-years in the placebo group). Estrogen plus progestin reduced the observed hip and clinical vertebral fracture rates by one third compared with placebo, both nominally significantly. The reductions in other osteoporotic fractures (23%) and total fractures (24%) were statistically significant (all associated CIs exclude 1).

The global index showed a nominally significant 15% increase in the estrogen plus progestin group (170 vs 151 per 10000 person-years). There were no differences in mortality or cause of death between groups (TABLE 3).

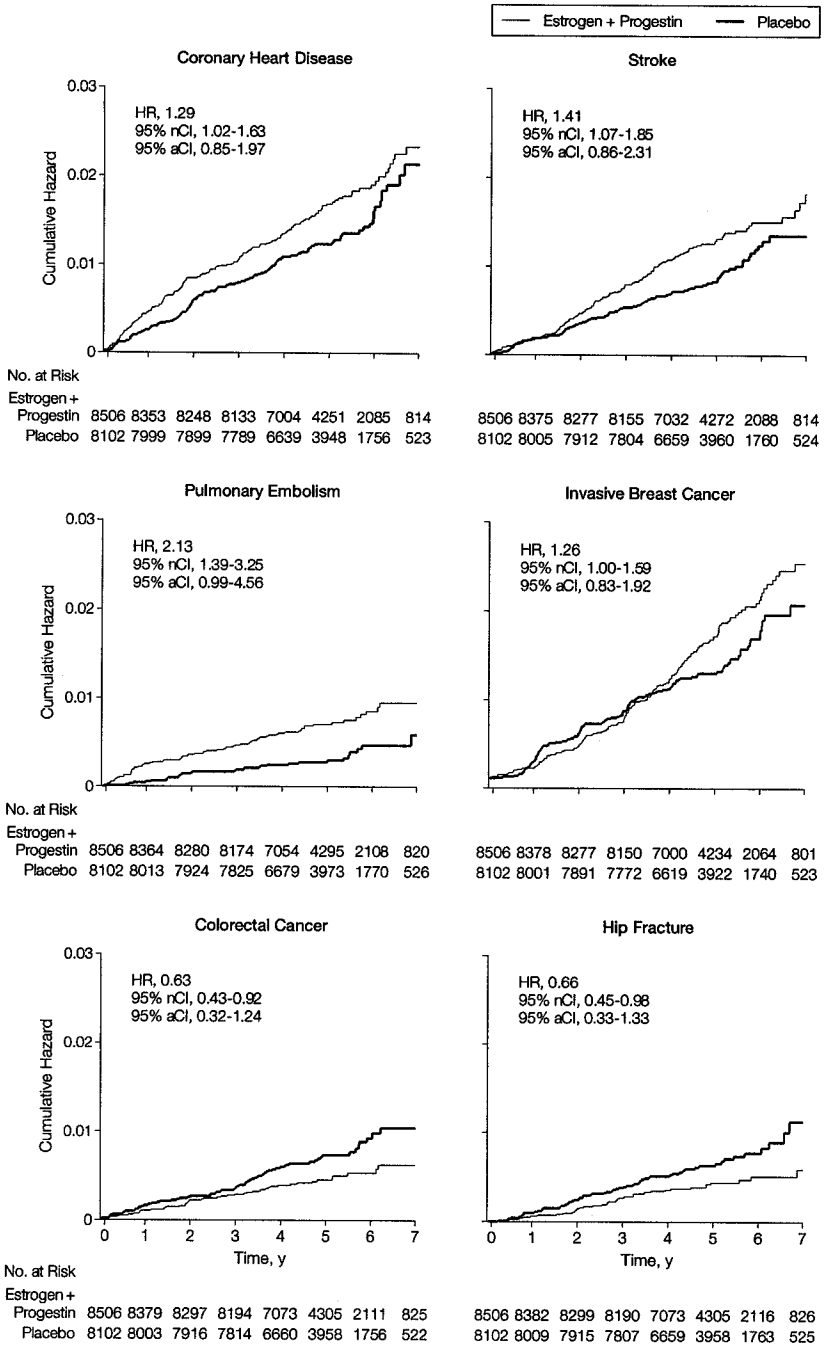
Time Trends

The Kaplan Meier estimates of cumulative hazards (FIGURE 3) for CHD indicate that the difference between treatment groups began to develop soon after randomization. These curves provide little evidence of convergence through 6 years of follow-up. The cumulative hazards for stroke begin to diverge between 1 and 2 years after randomization, and this difference persists beyond the fifth year. For PE, the curves separate soon after randomization and show continuing adverse effects throughout the observation period. For breast cancer, the cumulative hazard functions are comparable through the first 4 years, at which point the curve for estrogen plus progestin begins to rise more rapidly than that for placebo. Curves for colorectal cancer show benefit beginning at 3 years, and curves for hip fracture show increasing cumulative benefit over time. The difference in hazard rates for the global index (FIGURE 4) suggests a gradual increase in adverse effects compared with benefits for estrogen plus progestin through year 5, with a possible narrowing of the difference by year 6; however, HR estimates tend to be unstable beyond 6 years after randomization. Total mortality rates are indistinguishable between estrogen plus progestin and placebo.

Tests for linear trends with time since randomization, based on a Cox proportional hazards model with a time-

dependent covariate, detected no trend with time for CHD, stroke, colorectal cancer, hip fracture, total mortality, or the global index (TABLE 4). There was some evidence for an increasing risk of breast cancer over time with estrogen plus progestin ($z=2.56$ compared with a nominal z score for statistical significance of 1.96) and a decreasing risk of VTE with time ($z=-2.45$). These results must be viewed cautiously because the number of events in each interval is modest, the data in later years are still incomplete, and later year comparisons are limited to women still at risk of their first event for that outcome.

Figure 3. Kaplan-Meier Estimates of Cumulative Hazards for Selected Clinical Outcomes



HR indicates hazard ratio; nCI, nominal confidence interval; and aCI, adjusted confidence interval.

Subgroup Analyses

Cardiovascular Disease. A small subset of women (n=400; average follow-up, 57.4 months) in WHI reported conditions at baseline that would have made them eligible for HERS, ie, prior MI or revascularization procedures. Among these women with established coronary disease, the HR for subsequent CHD for estrogen plus progestin relative to placebo was 1.28 (95% CI, 0.64-2.56) with 19 vs 16 events. The remaining women, those without prior CHD, had an identical HR for CHD (145 vs 106; HR, 1.28; 95% CI, 1.00-1.65). Few women with a history of VTE were enrolled, but these data suggest a possibility that these women may be at greater risk of future VTE events when taking estrogen plus progestin (7 vs 1; HR, 4.90; 95% CI, 0.58-41.06) than those without a history of VTE (144 vs 66; HR, 2.06; 95% CI, 1.54-2.76). For stroke, prior history did not confer additional risk (1 vs 5 in women with prior stroke; HR, 0.46; 95% CI, 0.05-4.51; 126 vs 80 with no prior stroke; HR, 1.47; 95% CI, 1.11-1.95). No noteworthy interactions with age, race/ethnicity, body mass index, prior hormone use, smoking status, blood pressure, diabetes, aspirin use, or statin use were found for the effect of estrogen plus progestin on CHD, stroke, or VTE.

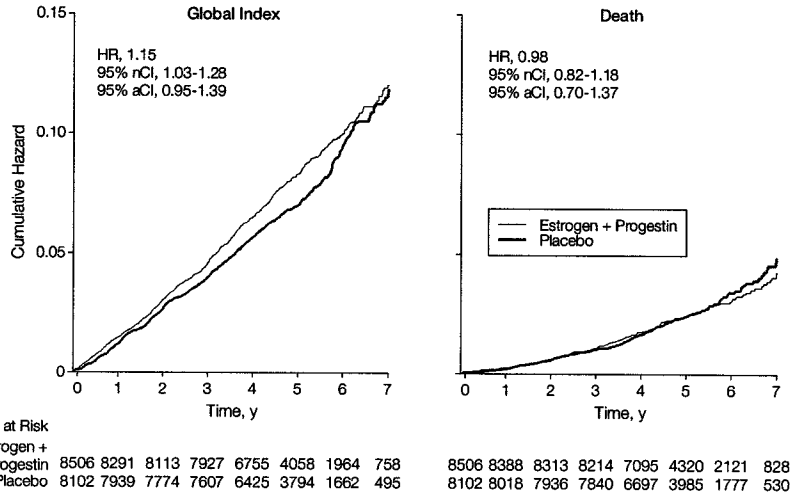
Breast Cancer. Women reporting prior postmenopausal hormone use had higher HRs for breast cancer associated with estrogen plus progestin use than those who never used postmenopausal hormones (among never users, 114 vs 102; HR, 1.06; 95% CI, 0.81-1.38; for women with <5 years of prior use, 32 vs 15; HR, 2.13; 95% CI, 1.15-3.94; for women with 5-10

years of prior use, 11 vs 2; HR, 4.61; 95% CI, 1.01-21.02; and for women with ≥10 years of prior use, 9 vs 5; HR, 1.81; 95% CI, 0.60-5.43; test for trend, $z=2.17$). No interactions between estrogen plus progestin and age, race/ethnicity, family history, parity, age at first birth, body mass index, or Gail-model risk score were observed for invasive breast cancer.

Further Analyses

Because a number of women stopped study medications during follow-up, several analyses were performed to examine the sensitivity of the principal HR estimates to actual use of study medications. Analyses that censored a woman's event history 6 months after becoming nonadherent (using <80% of or stopping study drugs) produced the largest changes to estimated effect sizes. This approach increased HRs to 1.51 for CHD, to 1.49 for breast cancer, to 1.67 for stroke, and to 3.29 for VTE. Analyses attributing events to actual hormone use ("as treated," allowing for a 6-month lag) produced more modest changes to these estimates. Analyses excluding women randomized during the period when the unopposed-estrogen component was open to women with a uterus and analyses stratifying by enrollment period did not substantially

Figure 4. Kaplan-Meier Estimates of Cumulative Hazards for Global Index and Death



HR indicates hazard ratio; nCI, nominal confidence interval; and aCI, adjusted confidence interval.

Table 4. Selected Clinical Outcomes by Follow-up Year and Randomization Assignment*

Outcomes	Year 1 E + P	Year 1 Placebo	Year 1 Ratio	Year 2 E + P	Year 2 Placebo	Year 2 Ratio	Year 3 E + P	Year 3 Placebo	Year 3 Ratio
No. of participant-years	8435	8050		8353	7980		8268	7888	
Coronary heart disease	43 (0.51)	23 (0.29)	1.78	36 (0.43)	30 (0.38)	1.15	20 (0.24)	18 (0.23)	1.06
Stroke	17 (0.20)	17 (0.21)	0.95	27 (0.32)	15 (0.19)	1.72	30 (0.36)	16 (0.20)	1.79
Venous thromboembolism	49 (0.58)	13 (0.16)	3.60	26 (0.31)	11 (0.14)	2.26	21 (0.25)	12 (0.15)	1.67
Invasive breast cancer	11 (0.13)	17 (0.21)	0.62	26 (0.31)	30 (0.38)	0.83	28 (0.34)	23 (0.29)	1.16
Endometrial cancer	2 (0.02)	2 (0.02)	0.95	4 (0.05)	4 (0.05)	0.96	4 (0.05)	5 (0.06)	0.76
Colorectal cancer	10 (0.12)	15 (0.19)	0.64	11 (0.13)	9 (0.11)	1.17	6 (0.07)	8 (0.10)	0.72
Hip fracture	6 (0.07)	9 (0.11)	0.64	8 (0.10)	13 (0.16)	0.59	11 (0.13)	12 (0.15)	0.87
Total death	22 (0.26)	17 (0.21)	1.24	30 (0.36)	30 (0.38)	0.96	39 (0.47)	35 (0.44)	1.06
Global index	123 (1.46)	96 (1.19)	1.22	134 (1.60)	117 (1.47)	1.09	127 (1.54)	107 (1.36)	1.13

Outcomes	Year 4 E + P	Year 4 Placebo	Year 4 Ratio	Year 5 E + P	Year 5 Placebo	Year 5 Ratio	Year 6 and Later E + P	Year 6 and Later Placebo	Year 6 and Later Ratio	z Score for Trend†
No. of participant-years	7926	7562		5964	5566		5129	4243		
Coronary heart disease	25 (0.32)	24 (0.32)	0.99	23 (0.39)	9 (0.16)	2.38	17 (0.33)	18 (0.42)	0.78	−1.19
Stroke	25 (0.32)	14 (0.19)	1.70	16 (0.27)	8 (0.14)	1.87	12 (0.23)	15 (0.35)	0.66	−0.51
Venous thromboembolism	27 (0.34)	14 (0.19)	1.84	16 (0.27)	6 (0.11)	2.49	12 (0.23)	11 (0.26)	0.90	−2.45
Invasive breast cancer	40 (0.50)	22 (0.29)	1.73	34 (0.57)	12 (0.22)	2.64	27 (0.53)	20 (0.47)	1.12	2.56
Endometrial cancer	10 (0.13)	5 (0.07)	1.91	1 (0.02)	4 (0.07)	0.23	1 (0.02)	5 (0.12)	0.17	−1.58
Colorectal cancer	9 (0.11)	20 (0.26)	0.43	4 (0.07)	8 (0.14)	0.47	5 (0.10)	7 (0.16)	0.59	−0.81
Hip fracture	8 (0.10)	11 (0.15)	0.69	5 (0.08)	8 (0.14)	0.58	6 (0.12)	9 (0.21)	0.55	0.25
Total death	55 (0.69)	48 (0.63)	1.09	41 (0.69)	44 (0.79)	0.87	44 (0.86)	44 (1.04)	0.83	−0.79
Global index	155 (1.96)	127 (1.68)	1.16	112 (1.88)	77 (1.38)	1.36	100 (1.95)	99 (2.33)	0.84	−0.87

*E + P indicates estrogen plus progestin. All outcome data are number of patients (annualized percentage).
†Tests for trends are based on Cox proportional hazards models with time-dependent treatment effects. The z scores shown indicate trends across all years.

affect the results. These analyses suggest that the intention-to-treat estimates of HRs may somewhat underestimate the effect sizes relative to what would be observed with full adherence to study medications.

COMMENT

The WHI provides evidence from a large randomized trial that addresses the important issue of whether most women with an intact uterus in the decades of life following menopause should consider hormone therapy to prevent chronic disease. The WHI enrolled a cohort of mostly healthy, ethnically diverse women, spanning a large age range (50-79 years at baseline). It is noteworthy that the increased risks for cardiovascular disease and invasive breast cancer were present across racial/ethnic and age strata and were not influenced by the antecedent risk status or prior disease. Hence, the results are likely to be generally applicable to healthy women in this age range. At the time the trial was stopped, the increases in numbers of invasive breast cancers, CHD, stroke, and PE made approximately equal contributions to harm in the estrogen plus progestin group compared with placebo, which were not counterbalanced by the smaller reductions in numbers of hip fractures and colorectal cancers.

Cardiovascular Disease

Even though the trial was stopped early for harm from breast cancer, a sufficient number of CHD events had occurred by 5.2 years of average follow-up to suggest that continuation to the planned end would have been unlikely to yield a favorable result for the primary outcome of CHD. Even if there were a reversal of direction toward benefit of a magnitude seen in the observational studies (ie, a risk reduction of 55%) during the remaining years, conditional power analyses indicate that less than 10% power remained for showing potential benefit if the trial continued.

The WHI finding that estrogen plus progestin does not confer benefit for preventing CHD among women with a uterus concurs with HERS findings among women with clinically apparent CHD,[10] with the Estrogen Replacement for Atherosclerosis trial, in which estrogen plus progestin did not inhibit progression,[23] and with a trial in women with unstable angina that did not observe a reduction in ischemic events.[24] The finding of an increased risk after initiation of treatment in WHI is similar to HERS. In HERS, after 4.1 and 6.8 years of follow-up, hormone therapy did not increase or decrease risk of cardiovascular events in women with CHD.[25] The WHI extends these findings to include a wider range of women, including younger women and those without clinically apparent CHD, and indicates that the risk may persist for some years.

Unlike CHD, the excess risk of stroke in the estrogen plus progestin group was not present in the first year but appeared during the second year and persisted through the fifth year. Preliminary analyses indicate that the modest difference in blood pressure between groups does not contribute much to an explanation of the increase in strokes (data not shown). The findings in WHI for stroke are consistent with but somewhat more extreme than those of HERS, which reported a nonsignificant 23% increase in the treatment group.[26] The results were also more extreme than those of the Women's Estrogen and Stroke Trial of estradiol (without progestin) in women with prior stroke, which found no effect of estrogen on recurrent strokes overall but some increase in the first 6 months.[27] Trials of the effect of estradiol on carotid intima-media thickness have yielded conflicting results.[28,29] At least 1 observational study has suggested that that use of estrogen plus progestin is associated with higher risk of stroke than estrogen alone.[14] In WHI, there was no indication that excess strokes due to estrogen plus progestin were more likely to occur in older women, in women with prior stroke history, by race/ethnicity, or in women with high blood pressure at baseline. Therefore, it appears that estrogen plus progestin increases the risk of strokes in apparently healthy women.

Venous thromboembolism is an expected complication of postmenopausal hormones, and the pattern over time in WHI is consistent with the findings from HERS and several observational studies.[30,31]

Cancer

The WHI is the first randomized controlled trial to confirm that combined estrogen plus progestin does increase the risk of incident breast cancer and to quantify the degree of risk. The WHI could not address the risk of death due to breast cancer because with the relatively short follow-up time, few women in the WHI have thus far died as a result of breast cancer (3 in the active treatment group and 2 in the placebo group). The risk of breast cancer emerged several years after randomization. After an average follow-up of about 5 years, the adverse effect on breast cancer had crossed the monitoring boundary. The 26% excess of breast cancer is consistent with estimates from pooled epidemiological data, which reported a 15% increase for estrogen plus progestin use for less than 5 years and a 53% increase for use for more than 5 years.[32] It is also consistent with the (nonsignificant) 27% increase found after 6.8 years of follow-up in HERS.[33]

With more common use of estrogen plus progestin, several epidemiological studies have reported that estrogen plus progestin appears to be associated with greater risk of breast cancer than estrogen alone.[34-37] In the PEPI trial, women in the 3 estrogen plus progestin groups had much greater increases in mammographic density (a predictor of breast cancer) than women in the estrogen or placebo groups.[38] In WHI, the HR for estrogen plus progestin was not higher in women with a family history or other risk factors for breast cancer, except for reported prior use of postmenopausal hormones. This may suggest a cumulative effect of years of exposure to postmenopausal hormones.

Endometrial cancer rates were low and were not increased by 5 years of es-

trogen plus progestin exposure. Close monitoring for bleeding and treatment of hyperplasia may contribute to the absence of increased risk of endometrial cancer.

The reduction in colorectal cancer in the hormone group is consistent with observational studies, which have suggested fairly consistently that users of postmenopausal hormones may be at lower risk of colorectal cancer.[39] The mechanisms by which hormone use might reduce risk are unclear. Results from other trials of postmenopausal hormones will help resolve the effects of hormones on colorectal cancer.[40]

Fractures

The reductions in clinical vertebral fractures, other osteoporotic fractures, and combined fractures supported the benefit for hip fractures found in this trial. These findings are consistent with the observational data and limited data from clinical trials[41] and are also consistent with the known ability of estrogen (with or without progestin) to maintain bone mineral density.[42] The WHI is the first trial with definitive data supporting the ability of postmenopausal hormones to prevent fractures at the hip, vertebrae, and other sites.

Overall Risks and Benefits

At the end of the trial, the global index indicated that there were more harmful than beneficial outcomes in the estrogen plus progestin group vs the placebo group. The monitored outcomes included in the global index were selected to represent diseases of serious import that estrogen plus progestin treatment might affect, and do not include a variety of other conditions and measures that may be affected in unfavorable or favorable ways (eg, gallbladder disease, diabetes, quality of life, and cognitive function). The data on these and other outcomes will be the subject of future publications. All-cause mortality was balanced between the groups; however, longer follow-up may be needed to assess the impact of the incident diseases on total mortality.

The absolute excess risk (or risk reduction) attributable to estrogen plus progestin was low. Over 1 year, 10000 women taking estrogen plus progestin compared with placebo might experience 7 more CHD events, 8 more strokes, 8 more PEs, 8 more invasive breast cancers, 6 fewer colorectal cancers, and 5 fewer hip fractures. Combining all the monitored outcomes, women taking estrogen plus progestin might expect 19 more events per year per 10000 women than women taking placebo. Over a longer period, more typical of the duration of treatment that would be needed to prevent chronic disease, the absolute numbers of excess outcomes would increase proportionately.

During the 5.2 years of this trial, the number of women experiencing a global index event was about 100 more per 10000 women taking estrogen plus progestin than taking placebo. If the current findings can be extrapolated to an even longer treatment duration, the absolute risks and benefits associated with estrogen plus progestin for each of these conditions could be substantial and on a population basis could account for tens of thousands of conditions caused, or prevented, by hormone use.

Limitations

This trial tested only 1 drug regimen, CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, in postmenopausal women with an intact uterus. The results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route. It remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile. The WHI findings for CHD and VTE are supported by findings from HERS, but there is no other evidence from clinical trials for breast cancer and colorectal cancer, and only limited data from trials concerning fractures.

Importantly, this trial could not distinguish the effects of estrogen from those of progestin. The effects of progestin may be important for breast cancer and atherosclerotic diseases, including CHD and stroke. Per protocol, in a separate and adequately powered trial, WHI is testing the hypothesis of whether oral estrogen will prevent CHD in 10739 women who have had a hysterectomy. The monitoring of this trial is similar to that for the trial of estrogen plus progestin. At an average follow-up of 5.2 years, the DSMB has recommended that this trial continue because the balance of overall risks and benefits remains uncertain. These results are expected to be available in 2005, at the planned termination.

The relatively high rates of discontinuation in the active treatment arm (42%) and crossover to active treatment in the placebo arm (10.7%) are a limitation of the study; however, the lack of adherence would tend to decrease the observed treatment effects. Thus, the results presented here may underestimate the magnitude of both adverse effects on cardiovascular disease and breast cancer and the beneficial effects on fractures and colorectal cancer among women who adhere to treatment.

The fact that the trial was stopped early decreases the precision of estimates of long-term treatment effects. A longer intervention period might have shown more pronounced benefit for fractures and might have yielded a more precise test of the hypothesis that treatment reduces colorectal cancer. Nonetheless, it appears unlikely that benefit for CHD would have emerged by continuing the trial to its planned termination. The trial results indicate that treatment for up to 5.2 years is not beneficial overall and that there is early harm for CHD, continuing harm for stroke and VTE, and increasing harm for breast cancer with increasing duration of treatment. This risk-benefit profile is not consistent with the requirements for a viable intervention for the primary prevention of chronic diseases.

Implications

The WHI trial results provide the first definitive data on which to base treat-

ment recommendations for healthy postmenopausal women with an intact uterus. This trial did not address the short-term risks and benefits of hormones given for the treatment of menopausal symptoms. On the basis of HERS and other secondary prevention trials, the American Heart Association recommended against initiating postmenopausal hormones for the secondary prevention of cardiovascular disease.[43] The American Heart Association made no firm recommendation for primary prevention while awaiting the results from randomized clinical trials such as WHI, and stated that continuation of the treatment should be considered on the basis of established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference.

Results from WHI indicate that the combined postmenopausal hormones CEE, 0.625 mg/d, plus MPA, 2.5 mg/d, should not be initiated or continued for the primary prevention of CHD. In addition, the substantial risks for cardiovascular disease and breast cancer must be weighed against the benefit for fracture in selecting from the available agents to prevent osteoporosis.

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EXHIBIT C

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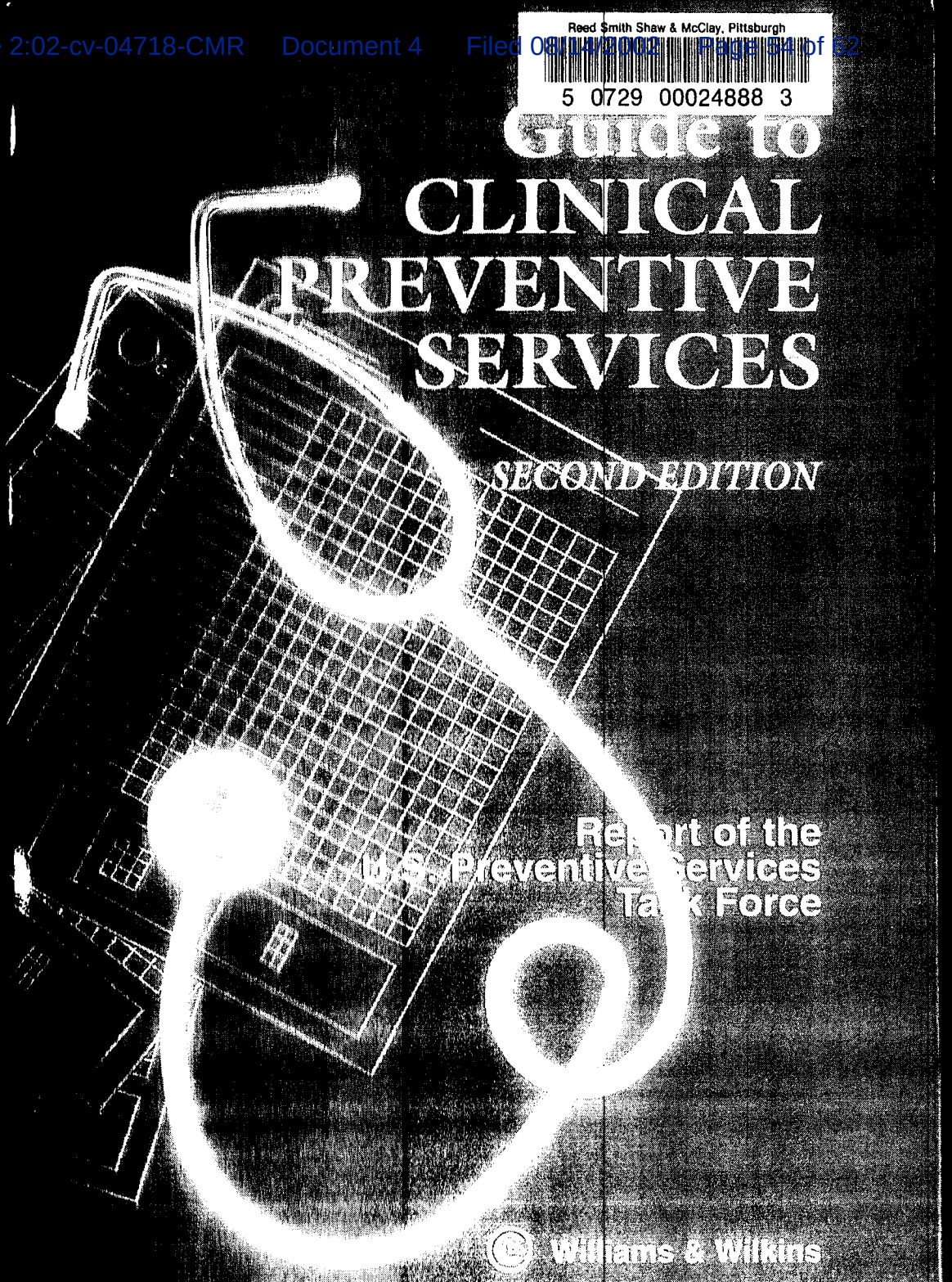
Guide to CLINICAL PREVENTIVE SERVICES

SECOND EDITION



Report of the U.S. Preventive Services Task Force

Williams & Wilkins

Guide to CLINICAL PREVENTIVE SERVICES

Report of the
U.S. Preventive Services
Task Force

SECOND EDITION

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7. Screening for Breast Cancer

RECOMMENDATION

Routine screening for breast cancer every 1–2 years, with mammography alone or mammography and annual clinical breast examination (CBE), is recommended for women aged 50–69. There is insufficient evidence to recommend for or against routine mammography or CBE for women aged 40–49 or aged 70 and older, although recommendations for high-risk women aged 40–49 and healthy women aged ≥70 may be made on other grounds (see Clinical Intervention*). There is insufficient evidence to recommend for or against the use of screening CBE alone or the teaching of breast self-examination.*

Burden of Suffering

In the U.S. in 1995, there were an estimated 182,000 new cases of breast cancer diagnosed and 46,000 deaths from this disease in women.[1] Approximately 32% of all newly diagnosed cancers in women are cancers of the breast, the most common cancer diagnosed in women.[1] The annual incidence of breast cancer increased 55% between 1950 and 1991.[2] The incidence in women during the period 1987–1991 was 110/100,000.[2] In 1992, the annual age-adjusted mortality from breast cancer was 22/100,000 women.[3] The age-adjusted mortality rate from breast cancer has been relatively stable over the period from 1930 to the present.[1,2] For women, the estimated lifetime risk of dying from breast cancer is 3.6%.[2] Breast cancer resulted in 2.2 years of potential life lost before age 65 per 1,000 women under age 65 in the U.S. during 1986–1988.[4] This rate was surpassed only by deaths resulting from motor vehicle injury and infections. Breast cancer is the leading contributor to cancer mortality in women aged 15–54,[1] although 48% of new breast cancer cases and 56% of breast cancer deaths occur in women age 65 and over.[2] As the large number of women in the "baby boom" generation age, the number of breast cancer cases and deaths will increase substantially unless age-specific incidence and mortality rates decline.

Important risk factors for breast cancer include female gender, residence in North America or northern Europe, and older age.[5] In American women, the annual incidence of breast cancer increases with age: 127

substantial benefit or harm from screening is not excluded by the preliminary data. Concerns regarding the early quality of mammography of Canadian NBSS 1 also apply to this trial.[48] Long-term follow-up and additional studies are needed to confirm this apparent lack of an incremental benefit of mammography above a careful, thorough annual CBE. It is also unclear whether CBE adds benefit to screening with mammography. A meta-analysis of mammography trial results reported similar reductions in breast cancer mortality with and without the addition of CBE.[42]

Evidence for effectiveness of BSE alone is also limited. In the United Kingdom Trial of Early Detection of Breast Cancer, a nonrandomized community trial, 40–50% of women living in two districts participated in BSE instruction that included a short film and a lecture by a specially trained health provider.[57] At 7-year follow-up, there was no reduction in breast cancer mortality in the BSE communities compared with the control districts. Baseline comparability of intervention and control districts, treatment variation by community, and contamination by other screening modalities were not assessed, however. A World Health Organization (WHO) population-based randomized controlled trial in Leningrad comparing formal BSE instruction to no intervention in women aged 40–64 has reported increases in physician visits, referrals for further screening tests, and excisional biopsies in the intervention group at 5-year follow-up.[58] Breast cancer patients in the two groups did not differ in number, size, or nodal status of their tumors. Completeness of endpoint assessment is a concern in this study, given the lack of a national tumor registry. Follow-up through 1999 is planned for reporting mortality results. In a case-control study of women who had been diagnosed with advanced stage (TNM III or IV) breast cancer, there was no association between disease status and self-reported BSE.[59] Proficiency in practicing BSE, however, was reported as poor by both cases and controls. For the small group of women reporting thorough BSE compared to all others, the relative risk was 0.54 (95% CI, 0.30 to 0.98). A meta-analysis of pooled data from 12 descriptive studies found that women who practiced BSE before their illness were less likely to have a tumor of 2.0 cm or more in diameter or to have evidence of extension to lymph nodes.[60] The studies from which these data were obtained, however, suffer from important design limitations and provide little information on clinical outcome (i.e., breast cancer mortality). Retrospective studies of the effectiveness of BSE have produced mixed results.[27,61–63]

Recommendations of Other Groups

The American Cancer Society (ACS),[64] American College of Radiology,[65] American Medical Association,[66] American College of Obstetricians and Gynecologists (ACOG),[67] and a number of other organizations[65] recom-

mend screening with mammography every 1–2 years and annual CBE beginning at the age of 40, and annual mammography and CBE beginning at age 50.

The American Academy of Family Physicians (AAFP) recommends CBE every 1–3 years for women aged 30–39 and annually for those aged 40 and older, and mammography annually beginning at age 50;[68] these recommendations are currently under review. The American College of Physicians (ACP) recommends screening mammography every 2 years for women aged 50–74 and recommends against mammograms for women under 50 or over 75 years and baseline mammograms.[69] The ACP makes the same recommendations for high-risk women, unless the woman expresses great anxiety about breast cancer or insists on more intensive screening. The Canadian Task Force on the Periodic Health Examination recommends annual CBE and mammography for women aged 50–69 and recommends against mammograms in women under 50.[70] The National Cancer Institute states there is a general consensus among experts that routine mammography and CBE every 1–2 years in women aged 50 and over can reduce breast cancer mortality, and that randomized clinical trials have not shown a statistically significant reduction in mortality for women under the age of 50.[71]

Organizations that presently recommend routine teaching of BSE include the AAFP,[68] ACOG,[67] and ACS.[64] The recommendations of the AAFP are currently under review.

Discussion

At this time, there is little doubt that breast cancer screening by mammography with or without CBE has the potential of reducing mortality from breast cancer for women aged 50 through about 70. The benefit derived from biennial screening appears to be quite similar to the benefit derived from annual screening. Given this similarity in effectiveness, biennial screening is likely to have the added benefit of increased cost-effectiveness. The incremental value of CBE above mammography or vice versa is uncertain, although the Canadian NBSS 2[24] suggests that careful CBE may be as effective as mammography.

Evidence does not establish a clear benefit from screening in women aged 40–49. Only the Canadian NBSS 1[30] was designed to test the effectiveness of screening in this age group, however, and none of the trials had adequate power for subgroup analysis. If screening is in fact ineffective in younger women, one possible explanation is a lower sensitivity of mammography in younger women (see *Accuracy of Screening Tests*). Other possibilities include suboptimal screening intervals, differential (less aggressive) treatment offered to women with mammographically detected cancer, and

EXHIBIT D

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FOR IMMEDIATE RELEASE
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Contact: HHS Press Office
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HHS AFFIRMS VALUE OF MAMMOGRAPHY FOR DETECTING BREAST CANCER

HHS Secretary Tommy G. Thompson today announced an updated recommendation from the U.S. Preventive Services Task Force (USPSTF) that calls for screening mammography, with or without clinical breast examination, every one to two years for women ages 40 and over. This recommendation affirms HHS' existing position on the value of mammography.

"The federal government makes a clear recommendation to women on mammography: If you are 40 or older, get screened for breast cancer with mammography every one to two years," Secretary Thompson said. "While developing technology certainly holds the promise for new detection and treatment methods, mammography remains a strong and important tool in the early detection of breast cancer. The early detection of breast cancer can save lives."

The USPSTF published two earlier breast cancer screening recommendations, in 1989 and 1996, that both endorsed mammography for women over age 50. The USPSTF is now extending that recommendation to all women over age 40, but found that the strongest evidence of benefit and reduced mortality from breast cancer is among women ages 50-69. The recommendation acknowledges that there are some risks associated with mammography (false-positive results that lead to unnecessary biopsies or surgery), but that these risks lessen as women get older.

The National Cancer Institute (NCI) has also reaffirmed its support for mammography. "Early detection of cancer saves lives and we continue to recommend mammography for women in their 40s and older," said Andrew von Eschenbach, M.D., director of the NCI. "While we seek improved methods of diagnosis and treatment of breast cancer, today mammography remains an important part of our effort to save lives through early detection."

Breast cancer is the most common cancer among women in the United States. In 2001, an estimated 192,200 women were diagnosed with breast cancer, and 40,600 women died from the disease.

In addition to age, other factors may increase a woman's risk of breast cancer. The strongest risk factors are a family history of breast cancer in a mother or sister, having already been diagnosed with breast cancer, or having had a previous breast biopsy showing atypical hyperplasia (an irregular pattern of cell growth).

"Mammography is an important tool for detecting breast cancer," said Janet Allan, Ph.D., R.N., vice chair of the USPSTF. "Clinicians and women should discuss individual risk factors to determine when to have a first mammogram and how often to have them after that."

Today's USPSTF recommendation results largely from the review of eight randomized controlled trials

of mammography (four of mammography alone and four of mammography plus clinical breast examination) that have reported results with 11 to 20 years of follow up. These studies have all been published since the task force last addressed this issue in 1996.

The USPSTF also noted that there remains insufficient evidence to recommend for or against routine clinical breast examination alone as a screening tool for breast cancer and insufficient evidence to recommend for or against routinely teaching or performing routine breast self-examination. While these techniques detect some additional cancers, there were not enough data to determine whether they reduced deaths from breast cancer.

The USPSTF, the leading independent panel of private-sector experts in prevention and primary care, is sponsored by HHS' Agency for Healthcare Research and Quality (AHRQ) and conducts rigorous, impartial assessments of scientific evidence for a broad range of preventive services. The breast cancer screening recommendation and materials for clinicians and patients are available on the Web at *http://www.ahrq.gov/clinic/3rduspstf/breastcancer/* or by calling AHRQ's toll-free information clearinghouse at 1-800-358-9295.

A webcast of today's HHS announcement press conference will be made available by kaisernetwork.org, a free service of the Kaiser Family Foundation, after 5 p.m. today at *http://www.kaisernetwork.org/healthcast/hhs/21feb02*.

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Note: All HHS press releases, fact sheets and other press materials are available at *http://www.hhs.gov/news*.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing Defendant Wyeth's Motion to Dismiss the Complaint of Plaintiff Estelle Geller for Failure to State a Claim and the accompanying Memorandum of Law in Support has been served by first-class mail, postage prepaid, this 14th day of August, 2002, on the following counsel of record:

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